

December 6, 2021

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

Report on the Deliberation Results

Classification	Human cellular/tissue-based products 2. Human somatic stem cell-processed products
Non-proprietary Name	Human (autologous) oral mucosa-derived epithelial cell sheet using human amniotic membrane substrate
Brand Name	Sakracy
Applicant	Hirosaki Lifescience Innovation, Inc.
Date of Application	March 31, 2021 (Application for marketing)

Results of Deliberation

In the meeting held on December 6, 2021, the Committee on Regenerative Medical 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 should be fulfilled.

Approval Conditions

1. The applicant is required to disseminate the guidelines for the proper use of the product jointly prepared with academic societies concerned, hold seminars, and take any other necessary measures to ensure that the product be used by doctors with adequate knowledge and experience in limbal stem cell deficiency who have acquired adequate skills for the procedure and knowledge about complications associated with the procedure, at medical institutions with an established medical care system for limbal stem cell deficiency, and in compliance with the “Indication or Performance” and “Dosage and Administration or Method of Use.”
2. Because of a limited number of participants in the clinical studies, the applicant is required to conduct a drug use-results survey covering all patients treated with the product, in principle, until the end of the re-examination period, to understand the characteristics of patients treated with the product and promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product.

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

Review Report

November 18, 2021

Pharmaceuticals and Medical Devices Agency

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

Brand Name	Sakracy
Classification	Human cellular/tissue-based products, Human somatic stem cell-processed products
Non-proprietary Name	Human (autologous) oral mucosa-derived epithelial cell sheet using human amniotic membrane substrate
Applicant	Hirosaki Lifescience Innovation, Inc.
Date of Application	March 31, 2021

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medical product. Its primary component is a cultured autologous oral mucosal epithelial cell sheet package including an amniotic membrane substrate and an oral mucosal epithelial cell sheet, which comes with an oral mucosal tissue transport set, the secondary component. The cultured autologous oral mucosal epithelial cell sheet package, the primary component, includes an oral mucosal epithelial cell sheet produced from oral mucosal epithelial cells, which are isolated from the patient's own oral mucosal tissue, seeded and cultured on an amniotic membrane substrate prepared from human allogeneic amniotic membrane. The oral mucosal tissue transport set, the secondary component, is used for the transport of the oral mucosal tissue collected at medical institutions.

Application Classification (1-1) New regenerative medical product

Items Warranting Special Mention

Orphan regenerative medical product (Orphan Regenerative Medical Product Designation No. 20 of 2020 [*R2 sai*]; PSEHB/MDED Notification No. 0623-5 dated June 23, 2020, by the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of Cellular and Tissue-based Products

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Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in alleviating ocular surface adhesion in patients with limbal stem cell deficiency, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication or performance and dosage and administration or method of use shown below, with the following approval conditions.

Indication or Performance

Alleviation of adhesions on the ocular surface accompanying limbal stem cell deficiency

Dosage and Administration or Method of Use

1. Production of cell sheet

Pieces of oral mucosal tissue, 6 mm in diameter, are collected from 2 to 4 sites of the patient's intraoral buccal mucosa confirmed to be lesion- or inflammation-free. The collected oral mucosal tissue is delivered to the manufacturer using the oral mucosal tissue transport set.

2. Transplantation of cell sheet

Ocular surface adhesion is released, and conjunctival scar tissue is removed from the ocular surface wherever possible. The oral mucosal epithelial cell sheet is transplanted on the exposed ocular surface by a suture technique. The oral mucosal epithelial cell sheet may be cut into pieces to be transplanted on the non-corneal areas, depending on the degree and range of the adhesion. For an exposed ocular surface larger than the oral mucosal epithelial cell sheet, the transplantation of the oral mucosal epithelial cell sheet is preceded by amniotic membrane transplantation.

3. Post-transplant treatments

The following treatments are provided where necessary:

- Use of a therapeutic contact lens
- For patients with a primary disease other than ocular cicatricial pemphigoid, oral cyclosporine 2 to 3 mg/kg daily from the day after transplantation, with dose adjustment according to the symptoms
- For patients with a primary disease of ocular cicatricial pemphigoid, oral cyclosporine 2 to 3 mg/kg daily and oral cyclophosphamide 50 mg (on the anhydrous basis) once daily from the day after transplantation, with dose adjustment according to the symptoms

Approval Conditions

1. The applicant is required to disseminate the guidelines for the proper use of the product jointly prepared with academic societies concerned, hold seminars, and take any other necessary measures to ensure that the product be used by doctors with adequate knowledge and experience in limbal stem cell deficiency who have acquired adequate skills for the procedure and knowledge about complications associated with the procedure, at medical institutions with an established medical care system for limbal stem cell deficiency, and in compliance with the “Indication or Performance” and “Dosage and Administration or Method of Use”.
2. Because of a limited number of participants in the clinical studies, the applicant is required to conduct a drug use-results survey covering all patients treated with the product, in principle, until the end of the re-examination period, to understand the characteristics of patients treated with the product and promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product.

Review Report (1)

September 22, 2021

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

Product Submitted for Approval

Brand Name	Sakracy
Classification	Human cellular/tissue-based products, Human somatic stem cell-processed products
Non-proprietary Name	Human (autologous) oral mucosa-derived epithelial cell sheet using human amniotic membrane substrate
Applicant	Hirosaki Lifescience Innovation, Inc.
Date of Application	March 31, 2021

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medical product. Its primary component is a cultured autologous oral mucosal epithelial cell sheet package including an amniotic membrane substrate and an oral mucosal epithelial cell sheet, which comes with an oral mucosal tissue transport set, the secondary component. The cultured autologous oral mucosal epithelial cell sheet package, the primary component, includes an oral mucosal epithelial cell sheet produced from oral mucosal epithelial cells, which are isolated from the patient's own oral mucosal tissue, seeded and cultured on an amniotic membrane substrate prepared from human allogeneic amniotic membrane. The oral mucosal tissue transport set, the secondary component, is used for the transport of the oral mucosal tissue collected at medical institutions.

Proposed Indication or Performance

Stevens-Johnson syndrome, ocular cicatricial pemphigoid, and refractory ocular surface diseases including thermal and chemical injuries

Proposed Dosage and Administration or Method of Use

1. Production of cell sheet

Oral mucosal tissue is collected from the patient. The collected oral mucosal tissue is transported to a cell culture processing facility designated by the marketing authorization holder, where the cell sheet is produced.

2. Transplantation of cell sheet

Symblepharon is released, and proliferative subconjunctival tissue is removed to prepare the ocular surface. The sheet is transplanted on the exposed cornea or sclera. After the transplantation, a therapeutic soft contact lens is applied where necessary.

3. Post-transplant treatments

Oral cyclosporine 2 to 3mg/kg daily for approximately 2 to 4 weeks from the day after transplantation where necessary, with dose adjustment according to the patient’s symptoms; for patients with a primary disease of ocular cicatricial pemphigoid, oral cyclophosphamide 50 mg once daily for approximately 4 weeks from the day after transplantation where necessary, with dose adjustment according to the patient’s symptoms

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List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

Sakracy is a human somatic stem cell-processed product manufactured from oral mucosal epithelial cells which are isolated from the patient's own oral mucosal tissue, seeded and cultured on an amniotic membrane substrate prepared from human allogeneic amniotic membrane. Sakracy is transplanted onto the ocular surface of the patient with a refractory ocular surface disease who have adhesion accompanying limbal stem cell deficiency (LSCD) so that the oral mucosal epithelial cells will be engrafted and epithelized, leading to the repair of ocular surface abnormality. Sakracy is a combination product consisting of the following primary component and secondary components:

Primary component: Cultured autologous oral mucosal epithelial cell sheet package including an oral mucosal epithelial cell sheet produced from oral mucosal epithelial cells which are derived from the patient's own oral mucosal tissue, seeded and cultured on an amniotic membrane substrate prepared from human allogeneic amniotic membrane

Secondary component: An oral mucosal tissue transport set for the transport of the oral mucosal tissue collected at a medical institution

Sakracy is designated as the orphan regenerative medical product with the intended indication or performance of "limbal stem cell deficiency" dated June 23, 2020 (Orphan Regenerative Medical Product Designation No. 20 of 2020 [*R2 sai*]).

1.2 Development history etc.

LSCD is a group of disorders characterized by decreased or lost corneal epithelial stem cells in the corneal limbus at the border between the cornea and conjunctiva that occurs congenitally or after birth, which causes the conjunctival epithelium to migrate onto the cornea and cover the surface, resulting in corneal opacification and reduced vision. LSCD can be caused by extrinsic factors such as thermal and chemical injuries as well as intrinsic factors such as Stevens-Johnson Syndrome (SJS), ocular cicatricial pemphigoid (OCP), or by aniridia, a developmental anomaly.

The radical treatment of LSCD is corneal epithelium reconstruction or restoration by supplying epithelial cells capable of proliferation. Existing treatments of LSCD includes autologous corneal limbal transplantation, allogeneic corneal limbal transplantation, human (autologous) corneal limbus-derived corneal epithelial cell sheet transplantation that was approved for marketing in March 2020, and human (autologous) oral mucosa-derived epithelial cell sheet transplantation approved for marketing in June 2021. All these procedures are intended for corneal reconstruction or restoration. However, LSCD may be accompanied by the adhesion of fibrotic subconjunctival tissue to the ocular surface, for which a new therapeutic option is needed. Amniotic membrane transplantation is occasionally performed on sites where the conjunctival scar tissue has been removed from the ocular surface. However, amniotic membrane does not contain epithelial cells and can only be transplanted onto eyes with remaining corneal epithelial stem cells for the purpose of corneal epithelium reconstruction. Thus, amniotic membrane transplantation is considered an adjunctive treatment performed with the corneal limbal transplantation.

Table 2. In-process control tests in manufacturing process of cultured autologous oral mucosal epithelial cell sheet

Step	Test item
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

2.2 Safety evaluation of adventitious agents

2.2.1 Oral mucosal tissue

The oral mucosal tissue used as a raw material of Sakracy conforms to the Standards for Biological Ingredients (Ministry of Health, Labour and Welfare [MHLW] Ministerial Announcement No. 210, 2003).

2.2.2 Human allogeneic amniotic membrane

Donors of human allogeneic amniotic membrane used as a raw material of Sakracy are subjected to examination and interview (medical history, history of transplantation and blood transfusion, and health condition of the donor and fetus [neonate]) and an examination for infections by a serological or nucleic acid amplification technique (hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV], human T-cell leukemia virus [HTLV] 1, parvovirus B19 [PVB19], Treponema pallidum, gonorrhea, Chlamydia), [REDACTED], [REDACTED], all of which conform to the Standards for Biological Ingredients (MHLW Ministerial Announcement No. 210, 2003).

2.2.3 Biological ingredients other than oral mucosal tissue and human allogeneic amniotic membrane

Biological ingredients other than oral mucosal tissue and human allogeneic amniotic membrane used in the manufacturing process of Sakracy are human holo-transferrin, human apo-transferrin, porcine intestinal heparin, superoxide dismutase, bovine serum albumin (BSA), and catalase, all of which conform to the Standards for Biological Ingredients (MHLW Ministerial Announcement No. 210, 2003).

2.3 Manufacturing process development (comparability)

Major changes in the manufacturing process of Sakracy during development are shown below (Process A and the proposed commercial process, respectively).

From Process A to the proposed commercial process: Changes in [REDACTED] of [REDACTED] and [REDACTED] of [REDACTED]

Study 170901 used Sakracy manufactured through Process A. The change from Process A to the proposed commercial process did not cause a considerable change in the manufacture of cultured autologous oral mucosal epithelial cell sheet, and the comparability of quality between the pre- and post-change products has been demonstrated.

shelf life of the primary component is limited to 55 hours [see Section 3], the sterility test is specified to be performed using [REDACTED] on Days [REDACTED] to [REDACTED] as a specimen. In addition to the specifications at release, the sterility confirmatory test ([REDACTED]) is performed using [REDACTED] during a culture process of [REDACTED] days and [REDACTED] days collected at the release. The result of the sterility confirmatory test is available after the cell sheet is transplanted in the patient.

Table 5. Specifications for cultured autologous oral mucosal epithelial cell sheet package

Test item	Test method
Appearance	Visual inspection
Viable cell count and cell viability	[REDACTED]
[REDACTED] immunostaining	Immunostaining ([REDACTED])
Bacterial endotoxins test	The Japanese Pharmacopoeia
Mycoplasma test*1	Nucleic amplification test (General Information in the Japanese Pharmacopoeia)
Sterility test*2	[REDACTED]
Gene expression profiling*3	[REDACTED]

*1, Use [REDACTED] during a period of [REDACTED] days. The result is available [REDACTED].

*2, Use [REDACTED] on Days [REDACTED] to [REDACTED].

*3, Use [REDACTED]. The result is available [REDACTED].

Table 6. Specifications for oral mucosal tissue transport set

Test item	Test method
Appearance	Visual inspection
Sterility test	[REDACTED]
[REDACTED]	[REDACTED] *1

*1, [REDACTED]

2.R Outline of the review conducted by PMDA

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

3. Stability and Outline of the Review Conducted by PMDA

Table 7 shows an outline of the stability study of the cultured autologous oral mucosal epithelial cell sheet package.

Table 7. Stability study of cultured autologous oral mucosal epithelial cell sheet package

Number of batches	Process	Storage condition	Study period	Storage form
2	Process A	[REDACTED]°C-[REDACTED]°C	[REDACTED] hours	Primary container ([REDACTED] container and cap, [REDACTED] O-ring, [REDACTED] O-ring)
3	Process A	[REDACTED]°C-[REDACTED]°C	[REDACTED] hours	
1	Process A	[REDACTED]°C-[REDACTED]°C	[REDACTED] hours	
3	Proposed commercial process	[REDACTED]°C-[REDACTED]°C	[REDACTED] hours	
1	Proposed commercial process	[REDACTED]°C-[REDACTED]°C	[REDACTED] hours	

Because no clear changes were observed in quality attributes under any of the storage conditions in the stability study, a shelf life of 55 hours was proposed for the primary component when stored at 15°C to 20°C. For the stability of oral mucosal tissue transport set, the primary polypropylene container with a polyethylene lid to be used for the commercial product was demonstrated to ensure the sterility of the

set when stored at 2°C to 8°C for [REDACTED] days, and thus a shelf life of 20 days was proposed for the secondary component when stored at 2°C to 8°C.

3.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA has concluded that the storage conditions and shelf lives of the primary and secondary components are appropriately specified.

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

The applicant submitted the following data relating to the indication or performance of Sakracy: *In vitro* study results from an immunohistological analysis and gene expression profiling; and *in vivo* study results from a general toxicity study in cornea/conjunctival injury rabbit models which had undergone the transplantation of Sakracy cell sheet on the ocular surface. In addition, the applicant submitted reference data from a study in LSCD model rabbits which had undergone the transplantation of rabbit autologous oral mucosal epithelial cell sheet.

4.1 In vitro studies

4.1.1 Immunohistological analysis (Evaluation data 2-5, 2-40, and 2-42)

Sakracy was subjected to immunofluorescence staining to evaluate expression of the following: Human cell-specific protein ([REDACTED]), epithelial cellular cytoplasm markers ([REDACTED] and [REDACTED]), squamous cell surface marker ([REDACTED]), cell adhesion-related [REDACTED] ([REDACTED]), [REDACTED] markers ([REDACTED] and [REDACTED]), epithelial progenitor cell/stem cell markers ([REDACTED] and [REDACTED]), cell growth marker ([REDACTED]), and extracellular substrate component proteins ([REDACTED], [REDACTED], [REDACTED], and [REDACTED]). The oral mucosal epithelial cell layer of Sakracy was found to have cells positive for [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], and [REDACTED]; and the amniotic membrane substrate layer was found to express [REDACTED], [REDACTED], [REDACTED], and [REDACTED].

4.1.2 Gene expression profiling (Evaluation data 2-8)

Sakracy was analyzed for the expression of the following genes using [REDACTED]: Genes expressed in epithelial cells including [REDACTED] ([REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], and [REDACTED]), and [REDACTED]; genes of epithelial progenitor cell/stem cell markers related to cell growth activity ([REDACTED], [REDACTED], [REDACTED], and [REDACTED]); and genes of mucous (viscous substance)-related markers ([REDACTED] and [REDACTED]). The analysis identified genes of [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], and [REDACTED] being expressed.

4.2 In vivo studies

4.2.1 Sakracy transplantation study in corneal/conjunctival injury rabbit models (Evaluation data 6-3)

Onto the left ocular surface with corneal/conjunctival epithelium of Kbl:JW rabbits removed by heptanol treatment, Sakracy cell sheet was transplanted, and the left eyeball was isolated on Days 3 and 15 of transplantation and evaluated for the survival of Sakracy cell sheet by [REDACTED]

() . Human cells derived from Sakracy were found to exist intermixedly with rabbit cells, indicating .

4.2.2 Study of autologous oral mucosal epithelial cell sheet transplantation in LSCD model rabbits (Reference data 4-3)

A rabbit LSCD model was developed using Kbl:JW rabbits, in which the epithelium of the cornea and conjunctiva including the corneal limbus was surgically removed followed by further clearance of the epithelium from that area. The conjunctival scar tissue was further surgically removed from the cornea of the rabbit LSCD model, a rabbit analogue cell sheet was produced from the oral mucosal tissue collected from the same animal for transplantation. The rabbit LSCD model in which the conjunctival scar tissue was removed from the cornea only was used as control. The corneal epithelium was evaluated for damage by fluorescein staining (staining of the epithelial cell-deficient area) 2 days after the removal of conjunctival scar tissue (Day 2) and at Weeks 1 and 2 and Months 1, 2, and 3. The size of epithelial cell-deficient area in the rabbits transplanted with the analogue cell sheets tended to be smaller than that in the control rabbits.

4.R Outline of the review conducted by PMDA

The applicant's explanation about the performance of Sakracy cell sheet:

In vitro studies of the immunohistological analysis and gene expression profiling identified the presence of epithelial cells expressing in an area where the oral mucosal epithelial cell sheet was transplanted, indicating that the epithelial cells contain stem cells with proliferating ability.

In addition, a histopathological examination on an eyeball transplanted with Sakracy cell sheet in the corneal/conjunctival injury rabbit models presented stained images showing layers of host-derived cells and Sakracy-derived oral mucosal epithelial cells mixing each other on the amniotic membrane substrate. Furthermore, the rabbit LSCD model transplanted with rabbit Sakracy cell sheet on the conjunctival-scar-tissue free cornea showed a tendency of smaller size of epithelial cell-deficient area than that in the model which had undergone only the removal of conjunctival scar tissue on the epithelial cell-deficient area.

In view of the above findings, the transplantation of Sakracy cell sheet is expected to supply oral mucosal epithelial cells that can survive and proliferate on the ocular surface of patients with a refractory ocular surface disease with LSCD-associated adhesion, ensuring a stable supply of these cells. When the survival and proliferation of oral mucosal epithelial cells lead to re-epithelialization of the ocular surface, the maintenance of adhesion-free condition or the prevention of re-adhesion would be possible.

PMDA's view:

Although the lack of results from the transplantation of Sakracy cell sheet in a disease model with ocular surface adhesion allows for only limited evaluation on the product performance in adhesion release, the applicant's explanation about the product performance is acceptable to some extent.

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

The applicant's explanation about the biological distribution of Sakracy cell sheet, based on results from the study on the transplantation of Sakracy cell sheet in corneal/conjunctival injury rabbit models (Evaluation data 6-3) and the follow-up¹⁾ results of Study 170901 (Evaluation data 7-1) in which Sakracy cell sheets were transplanted in patients with a refractory ocular surface disease with LSCD-associated adhesion:

Sakracy was transplanted on the left ocular surface in corneal/conjunctival injury rabbit models and its distribution in tissues²⁾ was investigated by [REDACTED] ([REDACTED]) [REDACTED]. Human cells derived from Sakracy cell sheet were observed at the transplantation site of the rabbit eyeball in 2 of 2 animals on Day 3 post-transplant and in 2 of 10 animals on Day 15 post-transplant. The number of human cells observed on Day 15 post-transplant was smaller than that on Day 3 post-transplant. On the other hand, no human cells were detected in tissues other than the cornea and conjunctiva, the transplantation site, at either timepoint. Accordingly, the possibility is extremely low that cells transplanted on the ocular surface are widely distributed in tissues in non-transplanted site.

In addition, in the follow-up of Study 170901 in which Sakracy cell sheets were transplanted in patients with a refractory ocular surface disease with LSCD-associated adhesion, the adhesion-free condition was maintained until Week 52 post-transplant. Patients included in Study 170901 had deficient corneal epithelium stem cells, in which the adhesion-free ocular surface is unlikely to be maintained unless epithelial cells are externally supplied even after the surgical release of adhesion. In view of this prospect, cells derived from Sakracy cell sheet are considered to have survived on the ocular surface and supplied oral mucosal epithelial cells over a period of 52 weeks.

5.R Outline of the review conducted by PMDA

PMDA's view:

Based on results from the study of transplantation of Sakracy cell sheet in the corneal/conjunctival injury rabbit models, the applicant's explanation is acceptable that cells in Sakracy cell sheet transplanted on to the ocular surface were unlikely to be distributed in tissues other than the cornea and conjunctiva.

The submitted data allow for only limited evaluation of the survival of Sakracy cell sheet and of the maintenance period. However, the adhesion-free condition was maintained until Week 52 post-transplant of Sakracy cell sheet in the Study 170901 follow-up, in which Sakracy was transplanted in patients with an ocular surface disease who were deficient in corneal epithelium stem cells, indicating that cells in Sakracy cell sheet can survive at the transplantation site for a certain period.

¹⁾ Follow-up investigation in all patients who completed Study 170901

²⁾ Heart, thoracic aorta, lung, trachea, liver, pancreas, gallbladder, tongue, salivary gland (parotid gland and submandibular gland), gastrointestinal tract (esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, and rectum), thymus, spleen, submandibular lymph node, mesenteric lymph node, kidney, urinary bladder, male reproductive organs (testis, epididymis, prostate gland, and seminal vesicle), female reproductive organs (vagina, uterus, and ovary), skin, mammary gland, pituitary gland, adrenal gland, thyroid gland, parathyroid gland, brain (cerebrum, cerebellum, and medulla oblongata), spinal cord, eyeball, accessory gland (lacrimal gland and accessory lacrimal gland), sciatic nerve, rectus femoris, bone, and bone marrow (sternum and femur)

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

The applicant submitted the following data relating to the non-clinical safety of Sakracy: general toxicity study in the corneal/conjunctival injury rabbit models transplanted with Sakracy cell sheets, tumorigenicity tests (a karyology test and a soft agar colony formation assay), biological safety study of the amniotic membrane substrate (study on subcutaneous implantation of the amniotic membrane substrate in nude rats, etc.), and safety studies of the oral mucosal epithelial cell sheet [REDACTED] and [REDACTED] (systemic toxicity study, intradermal dose study, and eye irritation test).

6.1 General toxicity study of Sakracy cell sheets transplanted on the ocular surface in corneal/conjunctival injury rabbit models (Evaluation data 6-3)

In this study in Kbl:JW rabbits, Sakracy cell sheet was transplanted on the left ocular surface with corneal/conjunctival epithelium removed by heptanol treatment, and necropsy was performed on Day 15 post-transplant. Lesions such as keratoconjunctivitis, corneal erosion, and ulcer were locally observed on the recipient eye (Table 8).

Table 8. General toxicity study of Sakracy transplanted on the ocular surface

Test system	Transplantation route	Observation period	Test product	Dose	Major findings
Corneal/ conjunctival injury rabbit models (both sexes)	Ocular surface	15 days	Sakracy cell sheet	1 piece/eye/ body	Transplantation site (eye): Loss of corneal transparency, neovascularization, conjunctival hyperemia, edema, discharge, corneal erosion, ulcer, and keratoconjunctivitis were observed in the non-transplantation and transplantation groups at conjunctival reaction and histopathological examination by the [REDACTED] method, and their frequency and severity tended to be higher (mild to moderate) in the transplantation group. Whole body: No toxicological changes

6.2 Other safety

6.2.1 Tumorigenicity test (Reference data 6-9)

A karyology test and a soft agar colony formation assay of epithelial cells isolated from Sakracy cell sheet were performed. Results summarized below brought to a conclusion that there were no findings suggestive of tumorigenicity of Sakracy. The applicant explained that they planned to collect information about the development of malignant tumors in the eyes in the post-marketing setting, although the clinical study has presented no findings suspected of neoplastic transformation.

- A karyology test was performed on 2 batches (TR9-CR-A and TR9-CR-B), which were cultured for a regular period ([REDACTED] weeks) and an extended period ([REDACTED] weeks). In 1 batch (TR9-CR-A), a specimen from the regular period culture presented karyotypic aberrations, but one from the extended period culture did not present any aberrations. In the other batch (TR9-CR-B), a specimen from the extended period culture presented karyotypic aberrations. For another batch (TR9-CR-C), a karyology test was not successful owing to a failure of cell growth during the culture period.
- The batch that presented karyotypic aberrations after the extended period culture (TR9-CR-B) was subjected to a soft agar colony formation assay. No anchorage-independent cell growth was detected, ruling out the possibility of enhanced cell growth that resulted from transformation.

- In the batch found unsuitable for the karyology test (TR9-CR-C), a specimen from the extended period culture was subjected to a soft agar colony formation assay, in which no anchorage-independent cell growth was observed.

6.2.2 Subcutaneous implantation study of the amniotic membrane substrate in nude rats (Evaluation data 6-5)

A circular sheet of the amniotic membrane substrate [REDACTED] mm in diameter was subcutaneously implanted in the back of male nude rats, and necropsy was performed [REDACTED] and [REDACTED] weeks after implantation. In this study, clinical observations, body weight measurement, hematology, clinical chemistry, urinalysis, necropsy, and gross and histopathological examinations on the implantation site were performed. At the transplantation site (subcutaneous), inflammation and granulation tissue were observed [REDACTED] and [REDACTED] weeks after implantation, but no tissue injury potential was indicated. No other abnormal changes were observed.

6.2.3 Safety evaluation of oral mucosal epithelial cell sheet [REDACTED] and [REDACTED] (Evaluation data 6-11 to 6-13)

To evaluate the safety of [REDACTED] and [REDACTED] ([REDACTED]) that remain in the final product, a systemic toxicity study, intradermal dose study, and eye irritation test were performed. Neither systemic toxicity nor irritation was observed. Of note, [REDACTED] prepared by diluting Sakracy with [REDACTED] [REDACTED] times was used as a test drug in all of the studies and tests.

6.2.3.1 Systemic toxicity study of oral mucosal epithelial cell sheet [REDACTED] in rats (Evaluation data 6-11)

A single dose of [REDACTED] or [REDACTED] ([REDACTED]) of Sakracy was intravenously administered to SD rats at [REDACTED] mL/kg followed by observation for up to [REDACTED] hours. No changes related to test drug administration were observed in any of the test drug groups.

6.2.3.2 Intradermal test of oral mucosal epithelial cell sheet [REDACTED] in rabbits (Evaluation data 6-12)

A single dose each of [REDACTED] or [REDACTED] ([REDACTED]) of Sakracy and physiological saline was intradermally administered to [REDACTED] sites on the back of Kbl:JW rabbits for each test drug at [REDACTED] mL per administration site ([REDACTED] sites in total) followed by observation for up to [REDACTED] hours. No changes suggestive of irritation were observed at any administration sites with the test drug.

6.2.3.3 Eye irritation test of oral mucosal epithelial cell sheet [REDACTED] in rabbits (Evaluation data 6-13)

A single dose of [REDACTED] or [REDACTED] ([REDACTED]) of Sakracy was administered to the conjunctival sac of Kbl:JW rabbits at [REDACTED] mL followed by observation for up to [REDACTED] hours. No changes suggestive of irritation on ocular mucosa were observed in any test drug groups.

6.R Outline of the review conducted by PMDA

PMDA's view:

Based on the submitted data and the following review, the clinical use of Sakracy will raise no particular problems from a toxicological viewpoint:

- No particular concerns about systemic safety are suggested because Sakracy cell sheet locally transplanted to the eye is highly unlikely to be distributed in tissues other than the eye [see Section 5] and no toxicological findings were noted in organs or tissues other than the eye [see Section 6.1].
- The findings from the general toxicity study on the local safety in the eye suggested the tolerability of Sakracy cell sheet transplanted on the ocular surface, the clinical application site, although Sakracy cell sheet survived on the ocular surface in only 2 of 10 animals until Day 15 post-transplant, the end of observation period [see Section 5], and the study provided limited information about the local safety in the eye. Oral mucosal epithelium, the starting material of Sakracy cell sheet, does not contain pluripotent cells, causing no genetic modifications, etc. in the manufacturing process of the product. Therefore, the product is considered to have a negligible risk of the local tumorigenicity in the eye. The *in vitro* tumorigenicity test presented no results suggestive of tumorigenicity [see Section 6.2.1]. Given these, no particular safety concerns are suggested.

The local safety in human eye is continuously discussed in Section “7.R.3 Safety.”

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

The applicant submitted evaluation data on the efficacy and safety from 1 clinical study and data from a clinical investigation under Advanced Medical Care B program presented in Table 9 as reference data.

Table 9. List of clinical studies for efficacy and safety

Data category	Region	Study identifier	Phase	Study population	N	Dosage regimen	Main endpoints
Evaluation	Japan	Study 170901	III	Patients with a refractory ocular surface disease with adhesion accompanying LSCD	7	A single transplantation with 1 Sakracy cell sheet after symblepharon release in the recipient eye and the removal of proliferative tissue from the conjunctiva and cornea	Efficacy Safety
Reference	Japan	Clinical investigation under Advanced Medical Care B program	-	Patients with a refractory ocular surface disease accompanied by severe LSCD	27	A single transplantation with Sakracy cell sheet analogue* after symblepharon release in the recipient eye and the removal of proliferative tissue from the conjunctiva and cornea	Efficacy Safety

* A product with the amniotic membrane substrate prepared by a different method and autologous oral mucosal epithelial cells cultured using medium ingredients and conditions different from Sakracy’s

7.1 Japanese phase III study (Evaluation data 7-1, Study 170901 [October 2018 to September 2019])

An open-label, uncontrolled, Japanese phase III study was conducted at 2 study centers to evaluate the efficacy and safety in patients with a refractory ocular surface disease with adhesion accompanying

LSCD of who had undergone the transplantation of Sakracy cell sheet (target sample size, 7 patients³⁾). Table 10 shows major inclusion and exclusion criteria.

Table 10. Major inclusion and exclusion criteria

Inclusion criteria	<p>Patients meeting all the following criteria:</p> <ul style="list-style-type: none"> • Patients with a refractory ocular surface disease (SJS, OCP, or thermal or chemical injury) accompanied by severe LSCD that is likely to result in a poor prognosis by corneal epithelium transplantation or unlikely to resolve with amniotic membrane transplantation alone • Patients who have a potential recipient eye with severe adhesion with the total adhesion score of ≥ 4 at screening • Patients ineligible for a therapeutic option of the transplantation of autologous tissue derived from the contralateral eye
Exclusion criteria	<p>Patients meeting any of the following criteria:</p> <ul style="list-style-type: none"> • Patients with active corneal infection or glaucoma with poor intraocular pressure control • Patients in whom the collection of oral mucosal tissue is considered difficult • Patients with diabetes mellitus with poor glycemic control (HbA1c $\geq 7.0\%$ at a screening test) • Patients infected with HIV, HCV, HBV, HTLV, or syphilis • Patients who have a target recipient eye that has already undergone the transplantation of a cultured autologous oral mucosal epithelial cell sheet (this treatment), have participated in a study of another study drug or regenerative medical product, or have a non-target recipient eye that has already undergone this treatment within the last 52 weeks.

The following method of use was employed.

From 2 to 4 sites of the patient’s buccal cavity mucosa, approximately 6-mm tissue pieces are collected 3 weeks before transplantation. The collected tissue pieces are cultured to prepare an oral mucosal epithelial cell sheet. The target recipient eye is treated for symblepharon release and the removal of proliferative subconjunctival tissue, and of abnormally proliferative tissue on the cornea if any, so that the corneal stroma and sclera are exposed. Where necessary, a micro sponge dampened with 0.04% mitomycin C (MMC) is placed subconjunctivally on the site of adhesion release for 4 minutes, then physiological saline is used to wash the surgical field before Sakracy cell sheet is transplanted on the field. To treat extensively deficient epithelial tissue, amniotic membrane may be concomitantly used as a graft. Concomitant cataract surgery may also be performed. After the transplantation, a therapeutic soft contact lens (SCL) is applied.

To adequately control inflammation on the ocular surface right after the surgery, a systemic immunosuppressive therapy is started according to the following dosage regimen as necessary in addition to systemic and local steroids. Furthermore, the patient receive a tear substitute or local hyaluronic acid preparation for tear substitution and local and/or systemic antimicrobial drugs for the prevention of infection. An antimicrobial eye ointment may be concomitantly used as appropriate.

- Oral cyclosporine 2 to 3 mg/kg daily for approximately 4 weeks from the day after transplantation, with dose adjustment according to the patient’s symptoms; for patients with a primary disease of OCP, oral cyclophosphamide hydrate (cyclophosphamide) 50 mg (on the anhydrous basis) once daily for approximately 4 weeks from the day after transplantation, in addition to the oral cyclosporine.

³⁾ The primary endpoint was change in the adhesion score at Week 24 post-transplant. Based on the expected value of the primary endpoint of 3 and the standard deviation (SD) of 1.7, the number of patients required to perform a one-sample t-test with a two-sided significance level of 5% and power of $\geq 80\%$ was calculated to be 6 patients. Taking potential drop-out into account, the target sample size was determined as 7 patients.

In this study, the period to the day of oral mucosa collection was defined as “before oral mucosa collection,” that from the day of oral mucosa collection to the day before transplantation as “epithelial sheet culture period,” and that from the day of transplantation to Week 24 of post-transplant as “evaluation period.” During the evaluation period, the ocular surface was rated according to the criteria presented in Table 11.

Table 11. Evaluation items on ocular surface and scoring criteria

	Endpoints	Scoring	
Conjunctival findings	Fornix shortening, upper	0: Normal depth 2: depth shortened by 25% to 50%	1: Depth shortened by <25% 3: Depth shortened by >50%.
	Fornix shortening, lower		
Corneal findings	Symblepharon	0: No symblepharon 2: Involving <1/2 of the corneal surface	1: Fornix shortening or strand formation 3: Involving ≥1/2 of the corneal surface
	Corneal keratinization	0: No corneal keratinization or involving just fornix 2: Involving 1/4 to 1/2 of the corneal surface	1: Involving <1/4 of the corneal surface 3: Involving ≥1/2 of the corneal surface
	Corneal epithelial defects	0: No epithelial defect 2: Involving 1/4 to 1/2 of the corneal surface	1: Involving <1/4 of the corneal surface 3: Involving ≥1/2 of the corneal surface
	Conjunctivalization (with connective tissues)	0: Absence of conjunctivalization 2: Involving 1/4 to 1/2 of the corneal surface	1: Involving <1/4 of the corneal surface 3: Involving ≥1/2 of the corneal surface
	Corneal neovascularisation	0: No neovascularization 2: Extending up to the pupil margin	1: Mild (confined to the corneal periphery) 3: Extending beyond the pupil margin
	Corneal opacification	0: Clear cornea with iris details clearly visualized 2: Moderate (lens details poorly seen with pupil margin visible)	1: Mild (pupil margin and lens visible) 3: Severe (complete obscuration of pupil margin)

All 7 patients enrolled underwent tissue collection and the transplantation of Sakracy cell sheet, and were included in the safety analysis and full analysis set (FAS). None of these patients discontinued the study, and all patients completed the evaluation at Week 24 post-transplant.

Causative etiologies of LSCD were SJS in 5 patients, OCP in 1 patient, and thermal or chemical injury in 1 patient. Table 12 shows patient characteristics.

Table 12. Patient characteristics

Subject number	Age	Sex	Recipient eye	Causative etiology of LSCD	Duration of disease	Ocular complication	Previous ophthalmic surgery (recipient eye)
1	42	Man	Left	Thermal or chemical injury	1 year and 7 months	-	Lamellar keratoplasty, 2 amniotic membrane transplantations, 2 surgeries for entropion
2	54	Man	Right	OCP	1 year	Steroid-induced glaucoma (both eyes)	-
3	77	Man	Right	SJS	37 years	Cataract (recipient eye)	-
4	59	Women	Left	SJS	8 years and 2 months	Cataract (recipient eye)	Surgery for entropion, amniotic membrane transplantation
5	50	Women	Left	SJS	42 years	-	-
6	49	Women	Right	SJS	27 years	-	Amniotic membrane transplantation, Cultured corneal epithelium sheet transplantation
7	28	Women	Right	SJS	1 year and 9 months	-	-

Table 13 shows results of the primary efficacy endpoint, change in the adhesion score⁴⁾ from baseline (from 7 days pre-transplant to the day of transplantation) to Week 24 post-transplant, rated by the data monitoring committee (central rating). A statistically significant decrease (improvement) was observed in the adhesion score ($P = 0.017$, one-sample t test).

Table 13. Change in adhesion score (central rating)

Subject number	Baseline	Week 24 post-transplant	Change from baseline
1	6	2	-4
2	8	7	-1
3	8	2	-6
4	8	5	-3
5	8	8	0
6	7	4	-3
7	9	8	-1
Mean ± SD	7.7 ± 1.0	5.1 ± 2.6	
Mean change from baseline [95% CI]			-2.6 [-4.5, -0.7]

In addition, results on main secondary endpoints are as shown below.

Table 14 shows the change in the adhesion score from baseline to Week 24 post-transplant rated by the investigator (hereinafter referred to as “investigator rating”).

⁴⁾ Total of scores for symblepharon and fornix shortening (upper and lower sacs), as rated according to Table 11. The central rating was conducted in through consultation among 3 doctors who were specialized in the treatment of the cornea and trained for adhesion scoring. They were blinded to subject information and timepoint of the examination (baseline or after transplantation).

Table 14. Change in adhesion score (investigator rating)

Subject number	Baseline	Week 24 post-transplant	Change from baseline
1	7	0	-7
2	8	5	-3
3	6	0	-6
4	6	1	-5
5	8	8	0
6	6	4	-2
7	9	8	-1
Mean ± SD	7.1 ± 1.2	3.7 ± 3.5	
Mean change from baseline [95% CI]			-3.4 [-5.9, -1.0]

At Week 24 post-transplant, 28.6% (2 of 7) and 42.9% (3 of 7) of the patients achieved the adhesion score of ≤ 3 according to the central and investigator ratings, respectively.

Table 15 shows the change in the ocular surface score⁵⁾ from baseline to Week 24 post-transplant.

Table 15. Change in ocular surface score

		Baseline ^{a)}	Week 24 of transplantation ^{a)}	Change from baseline [95% CI]
Ocular surface score	Central rating	15.6 ± 2.2	13.1 ± 4.3	-2.4 [-4.9, 0.0]
	Investigator rating	15.9 ± 2.2	11.0 ± 4.5	-4.9 [-7.4, -2.3]

a) Mean ± standard deviation (SD)

Table 16 shows the change in visual acuity⁶⁾ of the recipient eye from baseline to Week 24 post-transplant.

Table 16. Change in logarithmic minimum angle of resolution (LogMAR) visual acuity of recipient eye

		Baseline ^{a)}	Week 24 of transplantation ^{a)}	Change from baseline [95% CI]
LogMAR visual acuity	Distant visual acuity	+1.78 ± 0.71	+1.61 ± 0.88	-0.17 [-0.59, 0.26]
	Near visual acuity	+1.84 ± 0.63	+1.77 ± 0.90	-0.07 [-0.51, 0.37]

a) Mean ± SD

A quality-of-life (QOL) assessment using the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25), Japanese version v.1.4 (interviewer administered format) revealed that the mean ± standard deviation (SD) of change in the total score of subjective symptoms from baseline to Week 24 post-transplant was -0.34 ± 4.77 . Figure 1 shows a radar chart of the averages on subscales at baseline and Week 24 post-transplant.

⁵⁾ Total of scores on 8 items, symblepharon, fornix shortening (upper and lower sacs), corneal keratinization, corneal epithelium defect, invasion into conjunctiva, corneal neovascularisation, and corneal opacification, as rated according to Table 11

⁶⁾ The distant visual acuity was measured at 5 m using a 5-m visual acuity chart, and the near visual acuity was measured at 30 cm using a near visual acuity chart. When the visual acuity was measured to be <0.01 , visual acuity levels of counting fingers and hand motion were defined as 0.004 and 0.002, respectively (*Microincision Cataract Surgery* [in Japanese], Igaku-Shoin Ltd. 1994;161-173).

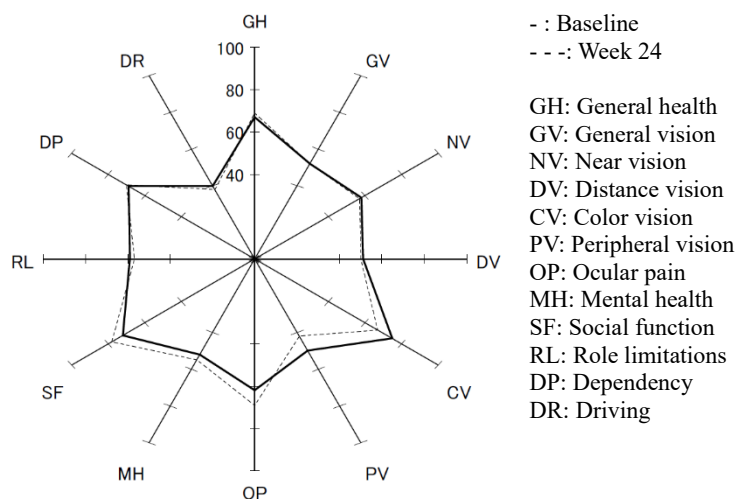


Figure 1. Radar chart of average scores on subscales of NEI VFQ-25 at baseline and Week 24 post-transplant

Adverse events⁷⁾ occurred in 7 of 7 patients (100%). Major adverse events were corneal epithelium defect in 4 patients (57%) and eye pain in 2 patients (29%). A causal relationship to Sakracy was ruled out for all the events. No deaths, serious adverse events, or malfunctions occurred.

7.2 Clinical investigation under Advanced Medical Care B program (Reference data 7-2 [July 2014 to September 2017])

An open-label, uncontrolled, clinical investigation was conducted at 2 study centers in Japan to evaluate the efficacy and safety of Sakracy analogue product⁸⁾ transplanted in patients with a refractory ocular surface disease accompanied by severe LSCD (target sample size, 30 patients).

The following method of use was employed.

Using tissue pieces collected from the patient's buccal cavity mucosa, a cultured oral mucosal epithelial cell sheet is prepared. The target recipient eye is treated for symblepharon release and the removal of abnormal proliferative tissue before Sakracy cell sheet is transplanted on the site. Where necessary, MMC is used and/or amniotic membrane transplantation is performed concomitantly. After the transplantation, a therapeutic SCL is applied. In addition to systemic and local steroids, systemic immunosuppressive therapy is started right after the surgery according to the following dosage regimen as necessary. Furthermore, the patient received tear substitution and local and/or systemic antimicrobial drugs for the prevention of infection.

- Oral cyclosporine 2 to 3 mg/kg daily from the day after transplantation, with dose adjustment according to the patient's symptoms; for patients with a primary disease of OCP, oral cyclophosphamide 50 mg (on the anhydrous basis) once daily from the day after transplantation, in addition to oral cyclosporine

⁷⁾ Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) Ver 22.1

⁸⁾ A product with an amniotic membrane substrate prepared by a different method and autologous oral mucosal epithelial cells cultured using medium ingredients and conditions different from Sakracy's

Of 27 patients enrolled, 22 patients were treated with the Sakracy analogue product except for 5 patients (failure of manufacture, etc.).

Adverse events occurred in 19 of 22 patients (86.4%) by Week 24 post-Sakracy analogue transplant. Major adverse events were corneal epithelium defect in 6 patients (27.3%), eye pain, symblepharon, constipation, and headache in 3 patients (13.6%) each, and eyelid oedema, abdominal pain upper, vomiting, and procedural pain in 2 patients (9.1%) each. No deaths occurred. Serious adverse events of corneal epithelium defect and cerebral haemorrhage occurred in 1 patient each, but a causal relationship to Sakracy analogue was ruled out for both events.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

Study 170901, which results were submitted as evaluation data for this application, was an open-label uncontrolled study. There were no agreed indicators for efficacy evaluation in the clinical studies for patient with a refractory ocular surface disease with adhesion accompanying LSCD. Given this situation, PMDA reviewed the efficacy evaluation of Sakracy with the following focus points:

Focus points

- The appropriateness of the conduct of Study 170901 as an open-label uncontrolled study
- The appropriateness of the primary endpoint
- The results of efficacy endpoints such as adhesion score

7.R.2 Efficacy

As a result of the review below, PMDA has concluded that the efficacy of Sakracy has been demonstrated to a certain extent in the treatment of a refractory ocular surface disease with adhesion accompanying LSCD.

7.R.2.1 Reason for conducting Study 170901 an open-label uncontrolled study

PMDA asked the applicant to explain the reason for conducting Study 170901 as an open-label uncontrolled study and the appropriateness of the efficacy evaluation based on the results from the uncontrolled study.

The applicant's explanation:

The reason for the uncontrolled study design

- Available treatment options for refractory ocular surface disease with adhesion accompanying LSCD include (a) allogeneic corneal limbal transplantation, (b) autologous corneal limbal transplantation or autologous corneal limbus-derived corneal epithelial cell sheet transplantation, and (c) amniotic membrane transplantation. None of these options were however considered appropriate as control treatment.
 - Allogeneic corneal limbal transplantation has obstacles of the lack of donors and frequent rejection (*Ophthalmology*. 2002;109:1278-84). Furthermore, the procedure is highly likely to induce prolonged corneal epithelium defect, and even a successfully epithelialized site can have a cicatricial progression in the long term, leading to the recurrence of decreased visual acuity, and

therefore these treatments have been reported as being subject to contraindications (*Clin Ophthalmol.* 2016;10:593-602).

- Autologous corneal limbal transplantation and autologous corneal limbus-derived corneal epithelial cell sheet transplantation are mainly indicated for unilateral LSCD because these operations require the collection of autologous normal corneal limbus. Study 170901 however targeted patients who did not have therapeutic options that use autologous tissue from the contralateral eye.
- Amniotic membrane transplantation, when performed alone in patients with LSCD or ocular surface adhesion, is likely to cause delayed epithelialization (*Br J Ophthalmol.* 2007;91:1042-47). A certain number of cases with eyes with symblepharon undergone amniotic membrane transplantation have been reported to have in re-adhesion (*Eye.* 2004;18:1251-57). Therefore, epithelial transplantation needs to be concomitantly performed to achieve adequate adhesion release by amniotic membrane transplantation (*Ocular Surf.* 2019;17:221-9).

The appropriateness of the use of results from uncontrolled studies for efficacy evaluation

- In patients with a chronic-stage refractory ocular surface disease with adhesion accompanying LSCD, visual acuity or adhesion is unlikely to improve without treatment (*Acta Ophthalmol.* 2014;92:447-53, *Eye.* 2009;23:1954-61, etc.). It would be possible to evaluate the efficacy of Sakracy by comparing the results of endpoints such as adhesion degree pre- and post-transplant.

The reason for the open-label study design

- It is practically difficult not to let doctors and patients know whether the surgical procedure using Sakracy has been performed.

PMDA accepted the above applicant's explanation and concluded that the conduct of Study 170901 as an open-label uncontrolled study is acceptable.

7.R.2.2 Appropriateness of the primary endpoint

The applicant's explanation about the reasons for specifying the adhesion score at Week 24 of the transplantation of Sakracy cell sheet as the primary endpoint and the clinical significance of improvement in adhesion score:

The reasons for specifying the adhesion score as the primary endpoint

- The transplantation using Sakracy is aimed to replace abnormal tissue of the ocular surface with intact epithelium and stabilize the adhesion-free ocular surface. Adhesion release will lead to better prognosis and visual acuity.
- The symblepharon score is an indicator established on the basis of analysis results on chronic eye lesion in patients with SJS. In these patients, symblepharon formation is a factor correlated to best-corrected visual acuity (*Ophthalmology.* 2007;114:1294-302). In addition, a clinical investigation in which an oral mucosal epithelial cell sheets were prepared using an amniotic membrane substrate and transplanted in patients with a refractory corneal/conjunctival disease reported that the symblepharon score is one of the factors correlated to improvement of best-corrected visual acuity at Week 24 post-transplant (*Ophthalmology.* 2013;120:193-200).

- To assess the effect of release (conjunctival sac reconstruction) from adhesion onto the conjunctival sac in the upper and lower eyelids, the fornix shortening (upper and lower) score was established. The conjunctival sac reconstruction enables the use of limbal-supported hard contact lens (HCL).
- Based on the above, it is possible to evaluate the efficacy of Sakracy by assessing the adhesion score, which is the sum of the symblepharon score and fornix shortening (upper and lower) score, in Study 170901.

The appropriateness of timing of efficacy endpoint evaluation

The evaluation timing of efficacy endpoint was specified as Week 24 post-transplant in view of the observations in a clinical investigation in which an oral mucosal epithelial cell sheets⁹⁾ were prepared using an amniotic membrane substrate and transplanted in patients with a refractory corneal/conjunctival disease, i.e., the ocular surface and symblepharon score were stabilized at Week 24 or later, and the condition of ocular surface up to Week 24 was related to the long-term prognosis; and there were no adverse events occurring specifically at Week 24 onward (*Br J Ophthalmol.* 2011;95:942-6, *Br J of Ophthalmol.* 2021;0:1-8).

Clinical significance of the improvement in adhesion score

Successful adhesion release achieved by the transplantation of Sakracy cell sheet, which is indicated for fornix shortening and symblepharon accompanying severe LSCD, leads to stabilized ocular surface, enabling cataract surgery, and lamellar keratoplasty for patients with severely opaque corneal stroma (*Ophthalmology.* 2013;120:193-200, *Am J Ophthalmol.* 2006;142:757-64). Patients with the adhesion score of ≤ 3 is allowed to use limbal-supported HCL, which can improve visual acuity indirectly (*Cornea.* 2020;39:S19-S27).

PMDA's view:

The transplantation using Sakracy is aimed to replace abnormal tissue of the ocular surface with intact epithelium and stabilize the adhesion-free ocular surface. The adhesion score was used as the primary efficacy endpoint of the transplantation of Sakracy cell sheet to treat ocular surface diseases with adhesion accompanying LSCD, which is understandable to some extent. The evaluation timing is also acceptable on the basis of findings from clinical investigation of the oral mucosal epithelial cell sheet using an amniotic membrane substrate, etc. For the reasons below, on the other hand, PMDA considers it also important to evaluate the efficacy not only based on the adhesion score but also taking account of the results of visual acuity correction and subjective symptoms that are expected to be improved by the adhesion release and additional treatment.

- The adhesion score has not been validated as an efficacy endpoint of treatment of LSCD and is not commonly used.
- The clinical significance of Sakracy is the improvement in prognosis that is achieved not only by improved adhesion score after transplantation but also by corrected visual acuity and improved subjective symptoms after adhesion release and subsequent additional treatment.

⁹⁾ A product prepared by investigators who conducted the investigator-initiated trial at early development stage, using the manufacturing process different from Sakracy's

In the following sections, PMDA evaluates the adhesion score and reviews other efficacy endpoints (visual acuity and subjective symptoms) for comprehensive evaluation.

7.R.2.3 Adhesion score

The applicant’s explanation about adhesion score results:

Table 17 shows change in the adhesion score of each patient in Study 170901. The mean changes in the centrally- and investigator-rated adhesion scores from baseline to Week 24 post-transplant [95% confidence interval (CI)] were -2.6 [-4.5, -0.7] and -3.4 [-5.9, -1.0], respectively, showing an improvement tendency in both ratings. In the follow-up study in all the patients who completed Study 170901, the mean changes in the centrally- and investigator-rated adhesion scores from baseline to Week 52 post-transplant [95% CI] were -2.1 [-4.0, -0.3] and -3.0 [-5.6, -0.4], respectively, showing the maintained improvement tendency in both ratings.

Table 17. Change in adhesion scores

Subject number	Central rating		Investigator Rating						
	Baseline	Week 24 post-transplant	Baseline	Post-transplant					
				Day 2	Week 4	Week 8	Week 12	Week 18	Week 24
1	6	2	7	0	0	0	0	0	0
2	8	7	8	3	4	4	4	4	5
3	8	2	6	3	0	0	0	0	0
4	8	5	6	1	1	1	1	1	1
5	8	8	8	0	0	7	7	7	8
6	7	4	6	0	0	0	1	2	4
7	9	8	9	0	1	1	1	8	8
Mean ± SD	7.7 ± 1.0	5.1 ± 2.6	7.1 ± 1.2	1.0 ± 1.4	0.9 ± 1.5	1.9 ± 2.7	2.0 ± 2.6	3.1 ± 3.3	3.7 ± 3.5

The improved adhesion scores were maintained from Day 2 to Week 4 post-transplant but declined over time at Week 8 onward. Subject 5 and 7 showed an 8-point decrease in the adhesion score from Day 2 to Week 24 post-transplant, which were considered possibly responsible for the declined mean score. A comparison between these 2 patients and the remaining 5 patients who maintained the improved score yielded the following observations that might have affected the outcome, which however do not deny the efficacy of Sakracy.

- In Subject 5 and 7, Sakracy cell sheet was transplanted only on the corneal area, and only amniotic membrane transplantation was performed for conjunctival adhesion release and the conjunctival sac reconstruction at the site from which abnormal tissue had been resected.
- In the remaining 5 subjects with the maintained improved adhesion score, on the other hand, not only amniotic membrane but also Sakracy cell sheet were transplanted for conjunctival sac reconstruction at the site that had undergone conjunctival adhesion release and abnormal tissue resection. In some of these subjects, cut pieces of Sakracy were transplanted at multiple sites.

The above information about use of Sakracy indicated that cut pieces of Sakracy might need to be transplanted on not only the corneal area but also the other areas depending on the degree and range of adhesion in patients requiring conjunctival sac reconstruction. Thus, such information will be provided to healthcare professionals appropriately using informative materials, etc.

PMDA's view:

The efficacy of Sakracy can be evaluated based on results from Study 170901, an open-label uncontrolled study [see Section 7.R.2.1], and results of the adhesion score, the primary endpoint, showed statistically significant improvement. According to the applicant explanation, based on results from the comparison between Subject 5 and 7, whose adhesion score decreased at Week 24, and the remaining 5 subjects, whose improved score was maintained, it is important that Sakracy cell sheet be transplanted onto an extensive area covering the conjunctival part to achieve adhesion release, depending on the area of adhesion. This explanation is acceptable. In view of the limited effect of conventional treatment on adhesion accompanying LSCD, which is likely to cause re-adhesion, the improved adhesion score at Week 24 after a single transplantation of Sakracy cell sheet documented in Study 170901 has certain clinical significance, and Sakracy has been shown to have a certain level of efficacy. The need of extensive use of Sakracy cell sheet, after being cut in pieces, to cover even non-corneal areas depending on to the degree and range of adhesion is important information related to the method of use of Sakracy to perform adhesion release effectively, and it is continuously discussed in Section "7.R.6 Dosage and Administration or Method of Use."

7.R.2.4 Reason for difference in adhesion score rating results between the investigator and data monitoring committee

The applicant's explanation:

At Week 24 of transplantation in Study 170901, more than half of the subjects showed inconsistency between centrally-rated and investigator-rated adhesion scores, which was particularly marked in Subject 4. Investigator-rated adhesion scores tended to be lower than central-rated scores.

The investigator assessment was conducted by doctors, in which a subject underwent examination and slit lamp microscopy for three-dimensional assessment. The central assessment, in contrast, was performed through consultation among 3 doctors based on photographs and videos to determine the final score. The investigator assessment could have given a low adhesion score when the transplantation using Sakracy clearly improved adhesion, judging a small residual adhesion as negligible, if any. In the central assessment, however, any change in adhesion pointed out by even 1 of 3 doctors could have been regarded as significant and affected the adhesion score.

Subject 4 had severe adhesion to the cornea mainly affecting the superior temporal field. The transplantation using Sakracy improved the condition of the adhesion site. At Week 24 post-transplant, adhesion was not observed in the front view, but was identified around the superior temporal field in the lateral nasal view. The investigator, considering that treating the residual adhesion in the superior temporal field was beyond the capability of the transplantation using Sakracy, and scored 1 only based on the adhesion in the inferior temporal field. In the central assessment, on the other hand, the adhesion in the inferior temporal field was recognized as symblepharon based on the thickness of adhesion affecting more than half the depth of the conjunctival sac. Along with the adhesion in the superior temporal field also being considered significant, the adhesion condition was scored 5. The inconsistency in the results of the central assessment and the investigator assessment is probably attributable to these factors.

PMDA's view:

The inconsistency in the adhesion scores between the investigator assessment and the central assessment, the former was made based on slit-lamp microscopic examination and the latter on still images and videos and by >1 doctors in a post hoc manner, is understandable to a certain extent. Given this, and in light of the tendency of overall improvement in the adhesion scores shown by both assessments [see Section 7.1], the inconsistency in rating results in individual subjects including Subject 4 has a minimal impact on the conclusion of the efficacy evaluation of Sakracy.

7.R.2.5 Visual acuity

The applicant's explanation about results on visual acuity:

Table 18 shows changes in visual acuity in each subject in Study 170901.

Table 18. Changes in corrected distant visual acuity (Landolt ring visual acuity test)

Subject number	Baseline		Week 12 post-transplant		Week 24 post-transplant	
	Decimal visual acuity	LogMAR	Decimal visual acuity	LogMAR	Decimal visual acuity	LogMAR
1	0.01	+2.00	Hand motion	+2.70	Hand motion	+2.70
2	0.1	+1.00	0.2	+0.70	0.3	+0.52
3	0.2	+0.70	0.4	+0.40	0.4	+0.40
4	0.03	+1.52	0.04	+1.40	0.03	+1.52
5	Counting fingers at 20 cm	+2.40	0.01	+2.00	0.01	+2.00
6	Counting fingers at 30 cm	+2.40	Counting fingers at 5 cm	+2.40	Counting fingers at 20 cm	+2.40
7	Counting fingers at 20 cm	+2.40	0.1	+1.00	0.02	+1.70
Mean ± SD	—	+1.78 ± 0.71	—	+1.51 ± 0.88	—	+1.61 ± 0.88

Visual acuity levels of counting fingers and hand motion were handled as 0.004 (LogMAR +2.40) and 0.002 (LogMAR +2.70) of decimal visual acuity, respectively.

Overall changes in corrected visual acuity after the transplantation of Sakracy cell sheet showed a tendency toward improvement. Subject 1, who had a history of 2 amniotic membrane transplantations and 1 lamellar keratoplasty to treat adhesion accompanied by LSCD after thermal or chemical injury, showed a slight reduction in visual acuity after the transplantation of Sakracy cell sheet. Subject 5 had 42-year-long SJS. Both Subjects 1 and 5 had been in poor pathological condition and had poor prognosis. In the remaining 5 subjects, corrected visual acuity remained unchanged or improved after transplantation.

Some subjects revealed inconsistency between the change in the adhesion score and that in corrected visual acuity. PMDA asked the applicant to discuss reasons for such inconsistency in each patient.

The applicant's explanation:

- Although the adhesion score was one of the factors related to visual acuity (*Ophthalmology*. 2007;114:1294-302, *Ophthalmology*. 2013;120:193-200), the corrected visual acuity is affected by ocular surface opacity, lens opacity, and the presence or absence of macular and/or optic nerve disease, etc., and thus improved adhesion score by Sakracy cell sheet transplantation does not always immediately lead to the improvement in corrected visual acuity.
- Subject 1 obtained better adhesion score at Week 24 post-transplant, but their visual acuity remained uncorrected. The subject had an adhesion that was not involving the pupillary zone, and the

transplantation of Sakracy cell sheet did not directly contribute to the correction of visual acuity. However, the ocular surface became stabilized after transplantation, and the recurrence of corneal epithelium defect was prevented.

- Subject 4 obtained better adhesion score at Week 24 post-transplant, but their visual acuity was not corrected. Because of symblepharon near the central cornea that was not completely covering the center, the transplantation of Sakracy cell sheet did not directly lead to the correction of visual acuity.
- Subject 7 failed to obtain better adhesion score but succeeded in visual acuity correction. Sakracy cell sheet was transplanted on the epithelial tissue on the cornea. The adhesion area surrounding the cornea was treated only with amniotic membrane transplantation but not with Sakracy. While the corrected visual acuity was improved by reduced opacity in the pupillary zone, the adhesion score once improved after transplantation and then declined at Week 24 post-transplant.

The applicant further conducted the follow-up study in all the patients who completed Study 170901 and presented the corrected visual acuity in each patient at Week 52 after the transplantation of Sakracy cell sheet (Table 19).

The applicant’s explanation about indirectly improved visual acuity by additional treatment after the transplantation of Sakracy cell sheet:

Table 19. Changes in corrected distant visual acuity (Landolt ring visual acuity test)

Subject number	Baseline		Week 52 post-transplant			
			Glass-corrected visual acuity		Limbal-supported HCL	
	Decimal visual acuity	LogMAR	Decimal visual acuity	LogMAR	Decimal visual acuity	LogMAR
1	0.01	+2.00	Hand motion	+2.70	-	-
2	0.1	+1.00	0.1	+1.00	-	-
3	0.2	+0.70	0.15	+0.82	0.8	+0.10
4	0.03	+1.52	0.04	+1.40	0.3	+0.52
5	Counting fingers at 20 cm	+2.40	Hand motion	+2.70	Hand motion	+2.70
6	Counting fingers at 30 cm	+2.40	Counting fingers at 5 cm	+2.40	Counting fingers at 5 cm	+2.40
7	Counting fingers at 20 cm	+2.40	0.02	+1.70	-	-

- The transplantation of Sakracy cell sheet contributed to the reconstruction of ocular surface to a near intact level, enabling 4 of 5 patients with an SJS-induced disease to use limbal-supported HCL. The best-corrected visual acuity (decimal visual acuity) of the recipient eye at baseline and Week 52 post-transplant improved from 0.2 to 0.8 in Subject 3 and 0.03 to 0.3 in Subject 4.
- The following are reported cases with oral mucosal epithelial cell sheet¹⁰⁾ transplantation using an amniotic membrane substrate:
 - A patient underwent a transplantation of the oral mucosal epithelial cell sheet using an amniotic membrane substrate and obtained better adhesion score, starting to wear a limbal-supported HCL that helps retain tear fluid or prevents its evaporation. Consequently, the patient’s corrected visual acuity improved (*Cornea*. 2020;39:S19-S27).

¹⁰⁾ A product prepared by investigators who conducted the investigator-initiated trial at the early development stage through a different manufacturing process from that of Sakracy

- Two patients with a corrected visual acuity of hand motion owing to adhesion accompanying LSCD and corneal stroma opacity underwent a transplantation of the oral mucosal epithelial cell sheet using an amniotic membrane substrate for adhesion release. Subsequent corneal transplantation and cataract surgery resulted in cleared cornea and improved visual acuity to approximately decimal 0.2 (*Am J Ophthalmol.* 2006;142:757-64).

In summary, the transplantation of Sakracy cell sheet on severe symblepharon involving the pupillary zone allows the adhesion to be released and is expected to improve or maintain the corrected visual acuity directly, while it also prevents non-severe adhesion from worsening. After adhesion release, the use of a limbal-supported HCL or a corneal transplantation on the stabilized ocular surface to treat corneal stroma opacity will give a chance to improve the corrected visual acuity.

PMDA's view:

Sakracy is primarily intended for the replacement of abnormal tissue on the ocular surface with intact epithelium to stabilize an adhesion-free ocular surface. The follow-up study of Study 170901 reported a case of improved corrected visual acuity by the use of limbal-supported HCL at Week 52 after the transplantation of Sakracy cell sheet, and another case of improved corrected visual acuity as a result of treatment for corneal opacification with an oral mucosal epithelial cell sheet transplantation using an amniotic membrane substrate followed by a corneal transplantation and a cataract surgery performed in stages. Taking account of these examples, the applicant's explanation is acceptable that the transplantation of Sakracy cell sheet stabilizes the ocular surface and allows for further treatment that gives a chance for visual acuity improvement. In Study 170901, however, data of patients who underwent the secondary surgeries after the transplantation of Sakracy cell sheet were not collected, and thus information about the clinical course of the secondary surgeries should be collected in the post-marketing setting.

7.R.2.6 Subjective symptoms (NEI VFQ-25 survey)

The applicant's explanation about evaluation results on subjective symptoms:

In Study 170901, the total score and sub-scale scores of NEI VFQ-25 did not show particular changes. Yet, scores on non-vision-related sub-scales of "General health" and "Ocular pain" as well as vision-specific sub-scales "Social functioning," "Mental health," and "Dependency" tended to show improvement. The transplantation of Sakracy cell sheets is therefore expected to reduce subjective symptoms.

No marked changes were seen in the total score in NEI VFQ-25 probably because the patients participated in the study primarily for the purpose of adhesion release, which resulted in insignificant improvement in visual acuity; patients with good visual acuity of the contralateral eye showed minimal changes in the NEI VFQ-25 score; and the sample size was as small as 7.

PMDA's view:

In Study 170901, the transplantation of Sakracy cell sheet was demonstrated to have an effect to release adhesion [see Section 7.R.2.3], and the transplantation of Sakracy cell sheet plus additional treatment were suggested to improve visual acuity [see Section 7.R.2.5]. Although how the treatment with Sakracy

influences improvement in subjective symptoms remains unclear, the applicant's views are acceptable that the treatment would not affect the conclusion on the efficacy evaluation and that adhesion release and improved visual acuity will lead to the improvement of subjective symptoms.

7.R.3 Safety

The safety review of Sakracy summarized in the following subsections did not reveal adverse events that may have been induced particularly by the use of Sakracy in the clinical study, albeit in the limited number of subjects. Accordingly, PMDA concluded that the safety profile of Sakracy does not raise particular concerns and that the safety is controllable through appropriate information provision to healthcare professionals about events observed in Study 170901 via informative materials, etc.

7.R.3.1 The occurrence of adverse events in Study 170901

The applicant's explanation about the safety of Sakracy:

In Study 170901, a total of 15 adverse events were reported from all 7 patients. Table 20 shows local adverse events in the eye. Non-ophthalmic events included vomiting, hepatic function abnormal, and dizziness in 1 patient (14.3%) each.

The study revealed no adverse drug reactions, malfunctions, deaths, serious adverse events, adverse events at oral mucosal tissue collection sites, or abnormal changes in clinical laboratory values reported as adverse events. This indicates that there is no particular safety problem.

Table 20. Local adverse events in the eye in Study 170901

	Recipient eye	Contralateral eye
All adverse events	7 (100.0)	2 (28.6)
Serious adverse events	0	0
Major adverse events		
Corneal epithelium defect	3 (42.9)	1 (14.3)
Eye pain	1 (14.3)	1 (14.3)
Calcinosis	1 (14.3)	0
Blepharitis allergic	1 (14.3)	0
Ocular discomfort	1 (14.3)	0
Eyelid pain	1 (14.3)	0
Ulcerative keratitis	1 (14.3)	0
Glaucoma	1 (14.3)	1 (14.3)

N (incidence, %)

Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) Ver 22.1

In view of corneal epithelium defect that occurred in recipient eyes in 3 patients and in contralateral eye in 1 patient, PMDA further reviews, in the following subsections, events potentially occurring in the treatment with Sakracy, with a focus on risks of events involving the cornea such as corneal epithelium defect.

7.R.3.2 Risk of adverse events involving the cornea such as corneal epithelium defect

PMDA asked the applicant to explain the clinical course of 4 patients who experienced corneal epithelium defect in Study 170901.

The applicant's explanation:

Clinical course of patients who experienced corneal epithelium defect

- Subject 1 had moderate corneal epithelium defect in the recipient eye. Because the subject underwent the transplantation of Sakracy cell sheet for adhesion release, the area of corneal epithelium defect, which had been observed before transplantation, was left untreated with Sakracy, and thus the corneal epithelium defect remained at the site after the procedure. Afterward, the corneal epithelium defect eventually healed without recurrence, resulting in stabilized ocular surface.
- Subject 3 had mild corneal epithelium defect in the contralateral eye and punctate staining in the contralateral eye at the site consistent with a protein-adhered area of hard contact lens, but no recurrence has been noted.
- Subject 5 had moderate corneal epithelium defect in the recipient eye and secondary mild ulcerative keratitis. The subject had a primary disease of SJS with Stage III LSCD, keratinization, and severe lacrimation decreased, which were predictive of postoperative corneal epithelium defect. After the transplantation of Sakracy cell sheet, corneal epithelium defect occurred. When the defect began to expand (Week 2), severe dry eye-associated drug toxicity was suspected, which improved and resolved as a result of less frequent use of eye drop.
- In Subject 7 had moderate corneal epithelium defect in the recipient eye. The subject had a primary disease of severe SJS. Postoperative inflammation on the ocular surface persisted. Multiple use of eye drops and a dry eye-associated corneal epithelium disorder were inferred to have complicated the pathological condition, resulting in corneal epithelium defect. The condition improved and resolved as a result of less frequency use of eye drops.

The applicant explained risks of cornea-related adverse events as follows, and also mentioned their intention to caution against adverse events via the package insert, provide information about the primary disease at ophthalmic surgeon seminars, and collect adverse event information via all-case surveillance.

Risks of cornea-related adverse events

- In Study 170901, post-transplant observation and examination were scheduled at Day 2 and Weeks 1, 2, 4, 8, 12, 18, and 24 post-transplant. The observation and examination of the cornea were performed up to 2 weeks post-transplant during hospitalization. After discharge from hospital, whenever subjective symptoms, etc. developed, the patient visited the office for a safety check. Punctate keratitis did not occur.
- For events observed in Study 170901 such as corneal epithelium defect, a causal relationship to the treatment with Sakracy was ruled out, and the majority of these events were considered attributable to the primary diseases.
- In terms of corneal melt, corneal ulcer, and corneal perforation secondary to corneal epithelium disorder, Study 170901 reported ulcerative keratitis in the recipient eye only in 1 patient (Subject 5), for which a causal relationship to the treatment with Sakracy was ruled out. The event resolved as described earlier.
- Study 170901 reported neither infective keratitis nor corneal infiltrates. These events are controllable with antimicrobial drugs, corneal protection drugs, etc [see Section 7.R.3.3].
- Oral mucosal epithelium is highly proliferative and is unlikely to cause epithalaxia. The oral mucosal epithelium is highly strong because of the susceptibility of oral cavity to external stimuli. The use of Sakracy is considered unlikely to cause a risk of prolonged corneal epithelium defect.

PMDA's view:

A causal relationship to Sakracy was ruled out for corneal epithelium defect in all cases reported, and all events resolved. The risks related to corneal epithelium defect are considered controllable with appropriate information provision. The applicant's explanation about the risk of cornea-related adverse events after use of Sakracy is acceptable. Nevertheless, cornea-related adverse events can be caused not only by Sakracy but also by their primary disease. Healthcare professionals should be provided with information about patient management strategies based on the characteristics of their primary disease in a specific and appropriate manner. Because of the extremely limited number of patients included in the clinical study, information should be continuously collected via post-marketing surveillance.

7.R.3.3 Risk of infections

PMDA asked the applicant to explain a risk of infection after the transplantation of Sakracy cell sheet, specifically, potential clinical concerns with corneal/conjunctival infections and endophthalmitis.

The applicant's explanation:

- The causes of corneal/conjunctival infections are not only the invasion in the ocular surface associated with the transplantation of Sakracy cell sheet but also include the use of concomitant drugs (immunosuppressive drugs, steroids, etc.) and dried ocular surface which are attributable to the primary disease. However, such conditions are controllable with a preoperative check for microorganisms on the ocular surface, pre- and postoperative antimicrobial medication, change in concomitant medication regimen, and other measures.
- The invasion associated with the use of Sakracy mainly involves the ocular surface and thus has no possibility to cause endophthalmitis. However, a concomitant cataract surgery, if performed, would pose a risk of postoperative endophthalmitis at a level comparable to a general cataract surgery.
- For patients receiving steroid eye drop for the treatment of OCP or SJS for a long period or experiencing hyperemia or eye discharge, a preoperative check for resistant microorganisms is recommended as in Study 170901.
- In addition to conventional pharmacovigilance activities, post-marketing surveillance will be conducted covering all patients who have been treated with Sakracy to collect adverse event information.

PMDA accepted the applicant's explanation about the risk of infections.

7.R.3.4 Adverse events attributable to concomitant drugs

PMDA asked the applicant to explain adverse events attributable to concomitant drugs.

The applicant's explanation:

- In Study 170901, concomitant drugs were used to suppress ocular surface inflammation according to the dosage regimens specified in the study protocol, which caused no adverse events of clinical concerns.

- Subject 2 had abnormal hepatic function at baseline. A causal relationship to cyclosporine and cyclophosphamide, systemically administered concomitant drugs, could not be ruled out, but the abnormality improved without treatment.
- Subject 2 had increased intraocular pressure in both recipient and contralateral eyes at baseline due to local steroid treatment. The condition was counted as glaucoma after the transplantation of Sakracy cell sheet, but improved in both eyes after changing of the drugs, etc.
- Information about the concomitant drugs (immunosuppressive drugs, steroids, etc.) used to prevent ocular surface inflammation for the transplantation of Sakracy cell sheet will be appropriately provided to healthcare professionals via the package insert and informative materials. Post-marketing surveillance will be conducted covering all patients treated with Sakracy to collect adverse event information.

PMDA's view:

Concomitant drug-associated adverse events may occur at a certain rate, but they are controllable with appropriate information provision.

7.R.3.5 Graft malfunction

PMDA asked the applicant to explain the possible concerns related to the malfunctions of Sakracy cell sheet, including poor survival, breakage and deviation of the graft, and the neoplastic transformation in the graft.

The applicant's explanation:

(a) Poor survival of the graft

Poor survival of the graft may be resulted from inadequate control of inflammation and therapeutic SCL falling off after the transplantation of Sakracy cell sheet. These are however considered controllable with postoperative treatment with antimicrobial drugs and anti-inflammatory drugs such as steroids.

(b) Breakage and deviation of the graft

Breakage and deviation of the graft are considered controllable with suture on the site of adhesion release using 10-0 nylon threads at the transplantation of Sakracy cell sheet and with the use of therapeutic SCL.

(c) Neoplastic transformation in the graft

No tumorigenicity of Sakracy cell sheet was observed in the non-clinical studies, or no events were suspected of neoplastic transformation in the clinical studies. Neoplastic transformation in the graft, however, requires the removal of cell sheet or can raise any other clinical concerns. Information about the concerned risk of neoplastic transformation in the graft will be appropriately provided to healthcare professionals via the informative materials, and post-marketing surveillance will be conducted covering all patients treated with Sakracy.

PMDA accepted the applicant's explanation about the risk of malfunctions of the graft.

7.R.4 Use of immunosuppressive drugs post-transplant

In Study 170901, the use of systemic immunosuppressive drugs was allowed as necessary after the transplantation of Sakracy cell sheet according to the dosage regimens presented below [see Section 7.1].

- Oral cyclosporine 2 to 3 mg/kg for approximately 4 weeks from the day after transplantation, with dose adjustment according to the patient's symptoms; for patients with primary disease of OCP, oral cyclophosphamide 50 mg once daily (on the anhydrous basis) for approximately 4 weeks from the day after transplantation, in addition to oral cyclosporine

The applicant's explanation about the use of immunosuppressive drugs after the transplantation of Sakracy cell sheet:

- Based on experience in the clinical investigation under Advanced Medical Care B program, the dosage regimens of cyclosporine and cyclophosphamide were specified in Study 170901.
- Sakracy is prepared from autologous cells and thus will not induce inflammation due to immune rejection. However, in patients with primary disease of SJS, OCP, etc., surgical invasion may trigger severe inflammation, possibly causing an epithelial disorder and scarring on the ocular surface. It is therefore important to suppress inflammation on the ocular surface with systemic cyclosporine and/or cyclophosphamide, which should be started right after the surgery.
- Whether to use cyclosporine is determined by the physician based on the presence or absence of inflammation (hyperemia) on the overall preoperative ocular surface. Although the dose increase of steroids without using cyclosporine is another option, the dosage regimen with reduced dose of steroids plus cyclosporine may help reduce drug adverse reactions of steroids and contribute to the prevention of postoperative adhesion. In Study 170901, all patients received cyclosporine at a daily dose of 2 to 3 mg/kg, which was adjusted as appropriate, for 39 (28-195) days (median [range] in 7 patients) from the day after transplantation. In the clinical investigation under Advanced Medical Care B program, some patients terminated the treatment before Week 4.
- The use of cyclophosphamide should be determined by the physician for patients with primary disease of OCP. OCP is an autoimmune disease targeting epithelial basal lamina, for which cyclophosphamide needs to be concomitantly administered with cyclosporine starting right after the surgery to suppress the immunoreaction adequately. Nevertheless, patients with OCP are mostly the elderly, and preferably the discontinuation of treatment should be considered for those with good control of postoperative inflammation in light of possible adverse drug reactions. In Study 170901, only 1 patient (Case KP-03) had a primary disease of OCP. The patient received cyclosporine at a daily dose of 2 to 3 mg/kg from the day after transplantation to Day 187¹¹⁾ and cyclophosphamide at a dose of 50 mg (on the anhydrous basis) once daily from the day after transplantation to Day 195,¹²⁾ while the doses were adjusted as appropriate.
- The efficacy of cyclosporine and cyclophosphamide was shown in the suppression of excessive inflammation at the transplantation site and contributed to the maintenance of the adhesion-free condition [see Section 7.R.2] based on the dosage regimen investigated.

¹¹⁾ Because of persistent inflammation in the ocular surface overall, the concomitant treatment was continued for >4 weeks.

¹²⁾ Because of persistent inflammation in the ocular surface overall, the concomitant treatment was continued for >4 weeks.

- Study 170901 reported no adverse events of cyclosporine and cyclophosphamide of potential clinical concerns [see Section 7.R.3.4].

PMDA's view:

The applicant points out the importance of the use of immunosuppressants against potential severe inflammation after the treatment with Sakracy in patients with a refractory ocular surface disease with adhesion accompanying LSCD caused by underlying SJS, OCP, etc., and that is acceptable. Based on results from Study 170901 in which immunosuppressants were administered after the treatment with Sakracy, the overall treatment with Sakracy including the use of immunosuppressants has promising efficacy with tolerable safety. In view of these findings, there is no problem in the use of immunosuppressants after the treatment with Sakracy according to the same dosage regimen used in Study 170901. However, because all patients received immunosuppressants for ≥ 4 weeks from the day after transplantation in Study 170901, the discussion continues in Section "7.R.6 Dosage and administration or method of use" on whether the use of immunosuppressants against potential inflammation on the ocular surface after the treatment with Sakracy should be limited to approximately 4 weeks from the day after transplantation.

7.R.5 Clinical positioning and indication or performance

The proposed "Indication or Performance" of Sakracy was "Stevens-Johnson syndrome, OCP, and refractory ocular surface diseases including thermal and chemical injuries."

On the bases of Sections "7.R.2 Efficacy" and "7.R.3 Safety" as well as the following reviews, PMDA concluded that the "Indication or Performance" section of Sakracy should be defined as follows.

Indication or Performance (Underline denotes additions, and strikethrough denotes deletions.)

Alleviation of adhesions on the ocular surface accompanying limbal stem cell deficiency ~~Stevens-Johnson syndrome, ocular cicatricial pemphigoid, and refractory ocular surface diseases including thermal and chemical injuries~~

7.R.5.1 Clinical positioning of Sakracy and target patients

The applicant's explanation about clinical positioning of Sakracy:

Conventional allogeneic corneal limbal transplantation, autologous corneal limbal transplantation, human (autologous) corneal limbus-derived corneal epithelial cell sheet transplantation, and human (autologous) oral mucosal epithelial cell sheet transplantation are treatments for LSCD that supply epithelial cells with proliferative capacity. In addition, scar tissue removal and amniotic membrane transplantation are adjunctive treatments used to improve the outcome of these conventional treatments. These procedures, however, have the following disadvantages.

Disadvantages in the conventional treatment of LSCD

- Allogeneic corneal limbal transplantation: Limited donor eyes are available. Due to its high rejection rate, postoperative immunosuppression is required for survival. Patients with SJS or severe thermal or chemical injury have extremely poor prognosis (*Ophthalmology*. 2002;109:1159-66, *Ophthalmology*. 2002;109:1278-84). Symblepharon is a prognostic factor that worsens the treatment

outcome (*Ophthalmology*. 2011;249:1697-704). The procedure has limited therapeutic effect because of the likely protracted postoperative corneal epithelium defect, which aggravates a cicatricial change over time, resulting in the recurrence of poor visual acuity.

- Autologous corneal limbal transplantation: For being a highly invasive procedure requiring 30% to 40% of the corneal limbus to be collected from the healthy eye (*BMJ Open Ophthalmol*. 2018;3:e000164), it is only indicated for a monocular disease. In addition, the procedure has been reported to have limited effect on releasing adhesion (*Br J Ophthalmology*. 2016;100:1416-20).
- Human (autologous) corneal limbus-derived corneal epithelial cell sheet transplantation: The procedure uses corneal limbal cells of the patient, thus it is mainly indicated for unilateral LSCD but not for LSCD caused by SJS or OCP (according to the package insert of Nepic). The adhesion releasing effect of human (autologous) corneal limbus-derived corneal epithelial cell sheets on has not been verified.
- The transplantation of corneal epithelium only (corneal limbal transplantation, keratoepithelioplasty, etc.): In patients with LSCD accompanied by ocular surface adhesion, these procedures are likely to result in poor epithelial extension, leading to prolonged corneal epithelium defect or corneal perforation. Even if the corneal epithelium is reconstructed, the graft may become dysfunctional. Prolonged corneal epithelium defect and corneal perforation are not expected to resolve spontaneously, and there is no treatment with established efficacy and safety at present (*Acta Ophthalmol*. 2014;92:e447-53, *Eye*. 2009;23:1954-61, etc.).
- Non-amniotic-membrane substrate-based human (autologous) oral mucosal epithelial cell sheet transplantation on fornix shortening: the absence of amniotic membrane-based substrate will preclude the survival and differentiation of epithelial cells on the exposed sclera (*Br J Ophthalmology*. 2001;85:567-75). This procedure, therefore, is considered to have limited effect in adhesion release.

Disadvantages in the concomitant treatments used with conventional treatment of LSCD

- Scar tissue removal, if performed alone to treat LSCD with ocular surface adhesion, would pose a risk of inflammation that can worsen the condition of ocular surface or cause the recurrence of adhesion. As a rule, therefore, surgical procedures are not performed without a concomitant epithelial transplantation.
- Amniotic membrane does not contain epithelial cells. If amniotic membrane alone is transplanted for the purpose of release adhesion, it would take time for epithelial cells around the amniotic membrane graft to grow to cover the amniotic membrane. This means that patients deficient in corneal epithelium stem cells cannot achieve corneal epithelialization by amniotic membrane transplantation alone and have a risk of re-adhesion (*Eye*. 2004;18:1251-7), requiring the transplantation of both amniotic membrane and epithelium (*Ocul Surf*. 2019;17:221-9). In some patients with OCP, fornix shortening without obvious corneal abnormality is observed (*Exp Ther Med*. 2020;20:3379-82). However, this pathological condition leads to Stage \geq II LSCD (*Cornea*. 2019;38:364-75) in 6 months to 1 year, for which amniotic membrane transplantation alone will not be effective.

In contrast, Sakracy has the following advantages that are not found in the conventional treatments and thus is available for diseases with adhesion which cannot be treated with these conventional treatments. Sakracy therefore can be recognized as a new therapeutic option.

Characteristics and advantages of the transplantation of Sakracy cell sheet for the treatment of LSCD

- Sakracy cell sheet is produced using autologous oral mucosal tissue and does not require the collection of corneal limbal tissue from the healthy eye, and causes no rejection.
- The amniotic membrane, the substrate of Sakracy cell sheet, has an anti-inflammatory and anti-scarring effects and promotes the survival of normal corneal/conjunctival epithelium (*Curr Eye Res.* 2000;20:173-7, *Biosci Rep.* 2001;21:481-9). The thick basal lamina of amniotic membrane acts as a strong supporting tissue and ensures a consistent supply of mucosal epithelium, and it hardly induces rejection due to its immune tolerance. Accordingly, Sakracy can also be indicated for patients with severe ocular diseases accompanied by intense inflammation on the ocular surface with severe dry eye and keratinization and be used for adhesion release in severe symblepharon cases.
- In patients with severely opaque corneal stroma, the transplantation of Sakracy cell sheet stabilizes the ocular surface so that a secondary lamellar keratoplasty is feasible. In patients with ocular surface adhesion and cataract, the use of Sakracy leads to adhesion release that, along with a conjunctiva resection as necessary, provides a surgical field for a safe cataract surgery (*Am J Ophthalmol.* 2006;142:757-64). Furthermore, adhesion release achieved with Sakracy will allow for the use of limbal-supported HCL, which is expected to improve visual acuity.

Accordingly, the “Indication or Performance” of Sakracy was initially proposed as “Stevens-Johnson syndrome, ocular cicatricial pemphigoid, and refractory ocular surface diseases including thermal and chemical injuries.” However, Sakracy can be also indicated for LSCD caused by “SJS, OCP, and refractory ocular surface diseases other than thermal and chemical injuries (graft versus host disease [GVHD], aniridia, idiopathic LSCD, recurrent pterygium, and conjunctival malignant tumor)” for the following reasons.

Pathological conditions suitable for the transplantation of Sakracy cell sheet

- Study 170901 enrolled 7 patients with severe LSCD (caused by SJS, OCP, and thermal and chemical injuries) who had a score ≥ 4 adhesion and demonstrated significant improvement in the adhesion score at Week 24 post-transplant.
- A clinical investigation (2002-2008) was conducted in patients with a refractory corneal/conjunctival disease, in whom an oral mucosal epithelial cell sheet with an amniotic membrane substrate¹³⁾ was transplanted. The investigation covered patients with LSCD not limited to those who had SJS, OCP, or thermal or chemical injuries but also those who had GVHD (1 patient), aniridia (1 patient), idiopathic LSCD (4 patients), malignant tumor (4 patients), or recurrent pterygium (2 patients). A retrospective analysis on 81 recipient eyes in 72 patients revealed that visual acuity and the adhesion score improved even in patients with a disease other than SJS, OCP, or thermal and chemical injuries (*Ophthalmology.* 2013;120:193–200, *Br J Ophthalmol.* 2021;0:1–8).
- Sakracy is indicated for LSCD classified as a refractory ocular surface disease that extensively affects the entire ocular surface and is accompanied by fornix shortening and/or symblepharon due to fibrotic subconjunctival tissue. Irrespective of the causative etiology, the ocular surface in such conditions has lost the Paliades of Vogt (POV) that should be observed in the normal corneal limbus, and presents a corneal epithelium disorder and ocular surface symptoms (*Ophthalmology.*

¹³⁾ Product prepared by investigators who conducted the investigator-initiated trial at early development stage, using the manufacturing process different from that for Sakracy

2014;121:2053-8). Sakracy has promising efficacy irrespective of the causative etiology, with its mechanism of action to supply mucosal epithelium to the ocular surface through the transplantation of oral mucosal epithelial cells with an amniotic membrane substrate. Furthermore, Sakracy can also be indicated for acute extensive LSCD with no adhesion or mild adhesion on the ocular surface for the purpose to control adhesion that can progress with severe inflammation.

Pathological conditions that were not investigated in Study 170901, i.e., GVHD, disease with congenitally abnormal corneal epithelial cytopoiesis (aniridia), idiopathic limbal stem cell deficiency, recurrent pterygium, and conjunctival malignant tumor.

As described below, all are causative etiologies of LSCD (*Cornea*. 2019;38:364-75), possibly accompanied by ocular surface adhesion, and do not pose any obstacle to the collection of normal oral mucosal tissue. Sakracy can be therefore indicated for all these pathological conditions.

- GVHD develops when donor's immune cells recognize autologous tissue as foreign substances after blood transfusion or allogeneic transplantation and activate cytotoxic immune responses targeting the autologous tissue. Chronic GVHD is complicated by ocular disorders including dry eye and painful keratoconjunctivitis, in which changes indicative of subconjunctival fibrogenesis such as fornix shortening and symblepharon are frequently observed (*Treatment Strategies for Corneal and Conjunctival Diseases* [in Japanese]. Igaku-Shoin Ltd; 2016:175-85). Chronic GVHD is reported to involve the oral cavity, presenting mucosal lichenoid lesion (*Biol Blood Marrow Transplant*. 2015;21:389-401), but another report showed successful adhesion release by the transplantation of an oral mucosal epithelial cell sheet prepared using an amniotic membrane substrate (*Br J Ophthalmol*. 2021;0:1-8).
- Aniridia is caused by haplo-insufficiency of *pax6* gene related to eyeball development and complicated by various ocular diseases such as iridial dysgenesis, keratopathy, and cataract. With the patient's growth, LSCD develops, resulting in reduced visual acuity. LSCD, if it develops, may be accompanied by ocular surface adhesion. Causative factors of abnormalities in the oral mucosal tissue have not been reported in the clinical practice guideline (Clinical practice guideline for aniridia [in Japanese]. *Journal of Japanese Ophthalmological Society*. Volume 125(1):38-76) or other literature (*Eur J Hum Genet*. 2012;20:1011-7).
- Recurrent pterygium is a disease with adhesion caused at the site where a pterygium was initially resected (a disease characterized by conjunctival and subconjunctival connective tissue growing and evolving from the nasal or temporal side toward the central cornea, which is treated with surgical resection) that can impair visual acuity and eye movement, and induce postoperative complications such as symblepharon and other adhesion-related changes (*Treatment Strategies for Corneal and Conjunctival Diseases* [in Japanese]. Igaku-Shoin Ltd; 2016:193-202, *Pterygium*. StatPearls Publishing. 2021). No causative factors of abnormal oral mucosal tissue have been reported (*Pterygium*. StatPearls Publishing. 2021).
- Conjunctival malignant tumor requires the complete resection of the lesion including its safety margin, which significantly damage intact ocular surface mucosa. The loss of corneal epithelium stem cells due to extensive resection causes corneal opacification, and the extensive conjunctival resection leads to reduced visual acuity due to severe adhesion (*Eye*. 2014;28:1131-35, *Ophthalmology*. 2014;121:994-1000). A conjunctival graft from the contralateral eye will not be

enough to cover the deficient area. A complete remission case by the transplantation of an oral mucosal epithelial cell sheet using an amniotic membrane substrate is reported (Strategic investigation for development of new regenerative medicine-based treatment methods for severe corneal diseases [in Japanese]. *The Medical Frontline*. 2007;62:132-80).

PMDA's view:

Study 170901 demonstrated that the transplantation of Sakracy cell sheet is effective in releasing ocular surface adhesion, and additional treatment after the adhesion release is expected to improve prognosis through the improvement of corrected visual acuity, etc. Sakracy, therefore, deserves recognition as a new therapeutic option to patients with LSCD accompanied by adhesion, which has been refractory to conventional treatments and postoperative management. Meanwhile, in view of the study population in Study 170901 that did not include patients with adhesion-free LSCD, the clinical benefits of Sakracy in patients with adhesion-free LSCD remains unknown, and thus the use of Sakracy is not recommended in such patient population. Accordingly, the "Indication or Performance" of Sakracy should be defined as "Release of ocular surface adhesion accompanying limbal stem cell deficiency."

The applicant explained that Sakracy is used to stabilize the ocular surface by supplying mucosal epithelium to an area affected by adhesive LSCD, and thus the treatment with Sakracy is expected to have efficacy irrespective of the causative etiology. The explanation is acceptable, and the target patient population of Sakracy not restricted by the causative etiology will pose no particular problems as long as tissue can be collected from the normal oral mucosa. Nevertheless, it is important that the treatment with Sakracy be performed appropriately in patients for whom adhesion release is expected to be clinically meaningful, because they are considered to deserve benefits from Sakracy. Accordingly, severity, etc. of ocular surface adhesion observed in patients in Study 170901 should be detailed in the "Clinical Studies" section in the package insert, and the following statement should be presented in the "Precautions Concerning Indication or Performance" section: Eligible patients must be selected by doctors with a full understanding of the information provided in the "Clinical Studies" section and of the efficacy and safety of Sakracy.

In addition, the severity of LSCD eligible for Sakracy is continuously reviewed in the following section.

7.R.5.2 Severity of LSCD

The applicant's explanation about severity of LSCD eligible for Sakracy:

Patients who underwent a transplantation using Sakracy or Sakracy analogue in Study 170901 and in the clinical investigation under Advanced Medical Care B program were largely classified as having Stage IIB or III LSCD according to the Stage classification (*Cornea*. 2019;38:364-75). However, some patients with Stage I LSCD were also included, indicating that even patients with LSCD of a low severity stage require the transplantation of Sakracy cell sheet depending on the degree of adhesion.

PMDA's view:

The stage classification of LSCD does not necessarily correspond to the degree of adhesion in terms of findings and the clinical course. The possibility cannot be denied that limiting the target patient population of Sakracy according to the stage classification of LSCD can deprive patients of the

opportunity for necessary treatment. Therefore, the severity of LSCD need not be specified in the “Indication or Performance” of Sakracy.

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

The proposed “Dosage and Administration or Method of Use” of Sakracy was specified based on Study 170901 as follows.

Dosage and Administration or Method of Use

1. Production of cell sheet

Oral mucosal tissue is collected from the patient. The collected oral mucosal tissue is transported to a cell culture processing facility designated by the marketing authorization holder, where the cell sheet is produced.

2. Transplantation of cell sheet

Symblepharon is released, and proliferative subconjunctival tissue is removed to prepare the ocular surface. The sheet is transplanted on the exposed cornea or sclera. After the transplantation, a therapeutic soft contact lens is applied where necessary.

3. Post-transplant treatments

Oral cyclosporine 2 to 3 mg/kg daily for approximately 2 to 4 weeks from the day after transplantation where necessary, with dose adjustment according to the patient’s symptoms; for patients with a primary disease of OCP, oral cyclophosphamide 50 mg once daily for approximately 4 weeks from the day after transplantation where necessary, with dose adjustment according to the patient’s symptoms

PMDA’s view:

Specifying the “Dosage and Administration or Method of Use” based on that in Study 170901, which demonstrated clinical benefits of Sakracy, is acceptable. Meanwhile, the following actions should be taken in describing the method of use of Sakracy:

- In Study 170901, sites of adhesion release and abnormal tissue removal were treated with not only Sakracy but also received amniotic membrane transplantation as necessary. An exposed ocular surface larger than the oral mucosal epithelial cell sheet needs to receive amniotic membrane transplantation in advance. This is important information in the method of use of Sakracy and should be clearly stated in the “Dosage and Administration or Method of Use.”
- To ensure effective adhesion release, cut pieces of Sakracy should be transplanted onto not only the corneal part but also the surrounding area, depending on the degree and range of adhesion. This is important information in the method of use of Sakracy [see Section 7.R.2.3] and should be clearly stated in the “Dosage and Administration or Method of Use.”
- As reviewed in Section “7.R.4 Use of immunosuppressive drugs post-transplant,” the use of immunosuppressants as necessary according to the dosage regimen used in Study 170901 has no problem. However, all the patients in Study 170901 received immunosuppressants for ≥ 4 weeks from the day after transplantation, and there is little need of limiting to approximately 4 weeks from the day after transplantation.

Furthermore, as a result of the review on the collection of oral mucosal tissue, treatment after the transplantation of Sakracy cell sheets, and the possibility of re-transplantation in the following subsections, PMDA concluded the “Dosage and Administration or Method of Use” of Sakracy should be described as below.

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

1. Production of cell sheet

Pieces of the Oral mucosal tissue, 6 mm in diameter, are ~~is~~ collected from 2 to 4 sites of the patient’s intraoral buccal mucosa confirmed to be lesion- or inflammation-free. The collected oral mucosal tissue is delivered to the manufacturer a cell culture processing facility designated by the marketing authorization holder, using the oral mucosal tissue transport set, where the cell sheet is produced.

2. Transplantation of cell sheet

Ocular surface adhesion-Symblepharon is released, and ~~proliferative~~ subconjunctival scar tissue is removed from the ocular surface wherever possible, to prepare the ocular surface. ~~The sheet~~ The oral mucosal epithelial cell sheet is transplanted on the exposed ocular surface by a suture technique cornea or sclera. The oral mucosal epithelial cell sheet may be cut into pieces to be transplanted on the non-corneal parts, depending on the degree and the range of the adhesion. For an exposed ocular surface larger than the oral mucosal epithelial cell sheet, the transplantation of the oral mucosal epithelial cell sheet is preceded by amniotic membrane transplantation. ~~After the transplantation, a therapeutic soft contact lens is applied where necessary.~~

3. Post-transplant treatments

The following treatments are provided where necessary:

• Use of a therapeutic contact lens

• For patients with a primary disease other than OCP, Cyclosporine is orally administered ~~oral cyclosporine~~ 2 to 3 mg/kg daily ~~for proximately 2 to 4 weeks~~ from the day after transplantation ~~where necessary~~, with dose adjustment according to the patient’s symptoms

• For patients with a primary disease of OCP, oral cyclosporine 2 to 3 mg/kg once daily and once-daily and oral cyclophosphamide 50 mg (on the anhydrous basis) once daily ~~for approximately 4 weeks from the day after transplantation where necessary~~, with dose adjustment according to the patient’s symptoms

7.R.6.1 Collection of oral mucosal tissue

The proposed “Dosage and Administration or Method of Use” does not specify the collection site of oral mucosal tissue. PMDA asked the applicant to explain the collection site of oral mucosal tissue in Study 170901 and present the applicant’s view on the collection site.

The applicant’s explanation about the collection site of the oral mucosal tissue in Study 170901:

- In Study 170901, the collection site of oral mucosal tissue was specified as area with intact mucosal tissue that was free from inflammatory lesions, and tissue was obtained from the buccal mucosa. In all patients, an adequate volume of the tissue was collected from the intact buccal mucosa, and the

post-procedural site healed favorably in general without causing any complications of safety concerns.

- It is important that the graft be non-keratinized tissue similarly to the normal cornea. Because mucosal tissue collection from the labium, vestibule of the mouth, or floor of the mouth potentially causes complications such as bleeding, nerve damage, mucous retention cyst owing to secretory gland injury, and periodontal disease, the buccal mucosa should be the first-choice collection site. Oral mucosal stem cells are present in the basal layer of mucosal epithelium, and thus the oral mucosal tissue should be obtained from the depth of the lamina propria mucosae so that it includes the entire mucosal epithelium stratum.
- In addition to SJS and OCP, GVHD may also affect the oral mucosa. Oral mucosal tissue cannot be collected from patients with inflammation or any lesion in oral mucosa, and such patients are not eligible for the treatment with Sakracy.

In view of the above, the package insert will provide cautionary advice that oral mucosal tissue be collected from the buccal mucosa free from lesions such as inflammation; healthcare professionals will be obligated to examine and record the patient's intraoral condition at screening; and precautions will be given to healthcare professionals, via informative materials, concerning the collection of mucosal tissue from patients with a disease affecting the oral mucosa.

In view of the possibility that doctors who are unfamiliar with intraoral procedures may perform oral mucosal tissue collection, PMDA asked the applicant to explain what information about the collection site of oral mucosal tissue will be provided to doctors, how such information will be provided, and a cooperation system with dentists, etc.

The applicant's explanation:

- For Study 170901, dentists and surgeons underwent a training for (a) plaque control and the management of intraoral environment before oral mucosa collection, (b) preoperative intraoral and extraoral disinfection and oral mucosa collection, and (c) postoperative management, using an oral mucosa collection manual.
- Informative materials about oral mucosa collection will be prepared to be distributed for the market launch of Sakracy, with similar contents to those used in Study 170901. The information will also include the following additional advice about the collection site: Collect tissue 1) at a sufficient distance from the opening of the parotid gland (parotid papilla), which location must be first visually confirmed; and 2) at the area of intact mobile mucosa around the mandibular molar anterior to the second molar region, in consideration of the buccal artery and nerve running in the area.
- Facilities for the transplantation of Sakracy cell sheet are required to have an established communication system with dentists and dental-oral surgeons to prepare for any arising procedural concerns and issues about oral mucosal tissue collection.

PMDA's view:

Study 170901 used oral mucosal tissue collected from the intraoral buccal mucosa free from lesions such as inflammation, and the collection site should be specified in the "Dosage and Administration or Method of Use." From a viewpoint of ensuring the collection of oral mucosal tissue with proper material

attributes, the “Precautions Concerning Dosage and Administration or Method of Use” section of the package insert should provide cautionary advice to the effect that mucosal tissue be obtained from the depth of the lamina propria mucosae to ensure that it includes the basal layer. The information should also be appropriately provided to healthcare professionals via informative materials.

The applicant explains that they will ensure the appropriate collection of oral mucosal tissue necessary for the production of Sakracy cell sheet through appropriate information provision, training of surgeons assuming the procedure, and seeking the establishment of a cooperation system between dentists or dental-oral surgeons and medical facilities implementing the treatment with Sakracy. PMDA considers these actions are appropriate.

7.R.6.2 Post-transplant treatments

PMDA asked the applicant to explain post-transplant treatments and precautionary measures.

The applicant’s explanation:

- In light of an approximately 8-week turnover interval of epithelium, the patient needs to wear a therapeutic SCL for 2 to 3 months post-transplant. If the SCL falls off soon after the transplantation, the epithelial graft may also fall off, potentially causing prolonged epithelium defect. Special attention should be paid to the SCL staying in the eye particularly for 2 weeks post-transplant.
- Patients with SJS, OCP, or GVHD on dry eye treatment should continue with the dry eye treatment after the transplantation of Sakracy cell sheet.
- Information about postoperative management (inflammation control, etc.) following the transplantation of Sakracy cell sheets will be appropriately provided to healthcare professionals via informative materials.
- Caution will be given in the package insert against adverse events of the treatment with Sakracy such as corneal epithelium defect.

PMDA’s view:

A certain number of the diseases eligible for the transplantation of Sakracy cell sheets are presumed to be associated with severe dry eye. After the treatment with Sakracy, treatments of dry eye and inflammation are important, and corneal epithelium defect also warrants careful attention. PMDA therefore has no particular objection to the applicant’s explanation about appropriate provision of information and cautions. In addition, the applicant’s explanation is acceptable that the use of a therapeutic SCL be continued after the transplantation of Sakracy cell sheet on the cornea until the epithelium is stabilized in 2 to 3 months.

7.R.6.3 Possibility of re-transplantation

PMDA asked the applicant to explain the possibility of relapse or recurrence of the primary disease causing re-adhesion on the site treated with Sakracy and the appropriateness of re-transplantation in such cases.

The applicant's explanation:

- SJS, OCP, GVHD, conjunctival malignant tumor, and recurrent pterygium may relapse or recur. SJS, OCP, or GVHD worsens with worsening ocular surface symptoms. Control of the primary disease is therefore important.
- A re-transplantation may be considered when the effect of the first transplantation has been attenuated due to the relapse or recurrence of a primary disease and re-adhesion has occurred. Because time from the successful first transplantation to a relapse or recurrence will be ≥ 1 year (*Br J of Ophthalmol.* 2021;0:1-8), the decision on whether to perform a re-transplantation will need to be made in 1 to 2 years.

PMDA's view:

There was no experience in the re-transplantation of Sakracy cell sheet in the clinical study, precluding the judgment on the appropriateness of the above criterion for re-transplantation. However, it is understandable that there will be some cases of re-adhesion due to the relapse or recurrence of primary disease after the treatment with Sakracy, which will require re-transplantation. The safety and efficacy of re-transplantation of Sakracy cell sheet should be collected in the 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 Sakracy:

The applicant plans post-marketing surveillance to evaluate the safety and efficacy of Sakracy in all patients treated with Sakracy in post-marketing clinical setting.

The safety specification of this surveillance includes data collection on all adverse events associated with the use of Sakracy.

The planned sample size for the surveillance is 200 patients per year in light of the expected number of patients using Sakracy in the post-marketing setting.

The follow-up period was specified as up to Week 24 post-transplant. Most adverse events in Study 170901 occurred during the period from the collection of the oral mucosal tissue to Week 24 post-transplant.

PMDA's view:

Because of extremely limited experience in the use of Sakracy and insufficient safety information of Sakracy, the post-marketing surveillance needs to cover all patients treated with Sakracy in the post-marketing setting to collect information about the safety and efficacy of Sakracy in a prompt and unbiased manner. The above applicant's explanation about the surveillance plan (safety specification, planned sample size for the surveillance, and follow-up period) has been accepted. Through the surveillance, information about causative etiologies and the success or failure in the production of Sakracy cell sheets should also be gathered. Information about the proper tissue collection for the production of Sakracy cell sheets should be provided to healthcare professionals in an appropriate and prompt manner, whenever available.

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)

Based on the data submitted, PMDA has concluded that Sakracy has a certain level of efficacy in the treatment of "Release of ocular surface adhesion accompanying limbal stem cell deficiency," and that Sakracy has acceptable safety in view of its benefits. Sakracy is clinically meaningful because it provides a new treatment option for patients with LSCD.

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

Review Report (2)

November 18, 2021

Product Submitted for Approval

Brand Name	Sakracy
Non-proprietary Name	Human (autologous) oral mucosa-derived epithelial cell sheet using human amniotic membrane substrate
Applicant	Hirosaki Lifescience Innovation, Inc.
Date of Application	March 31, 2021

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

As a result of the review in Section “7.R.2 Efficacy” of the Review Report (1), PMDA has concluded that Sakracy has a certain level of efficacy in the treatment of adhesion accompanying LSCD.

The above conclusion of PMDA was generally supported by the expert advisors at the Expert Discussion, while the following comments were raised:

- In patients with OCP, the degree of ocular surface adhesion depends on the stage of the disease. However, OCP-associated results were obtained only from Subject 2, indicating limitations in the evaluation in this review. Information about the efficacy and safety of Sakracy should be further collected through the post-marketing surveillance.

Taking account of comments raised at the Expert Discussion in Section “1.5 Post-marketing surveillance plan (draft),” PMDA concluded that information about the efficacy and safety of Sakracy including characteristics of the causative etiology should be further collected through the post-marketing surveillance.

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 Sakracy does not raise particular concerns. The product safety can be controlled by appropriate information provision about adverse events observed in Study 170901 to healthcare professionals through informative materials, etc.

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.5 Clinical positioning and indication or performance” of the Review Report (1), PMDA has concluded that the “Indication or Performance” of Sakracy should be defined as “Release of ocular surface adhesion accompanying limbal stem cell deficiency,” as shown in the mentioned section of the Review Report (1).

The following comments were raised from the expert advisors at the Expert Discussion:

- In Study 170901, Sakracy was used in patients with ocular surface adhesion accompanying LSCD, and thus Sakracy is intended for the treatment of ocular surface adhesion. It is appropriate to clearly mention “ocular surface adhesion” in the “Indication or Performance” of Sakracy in view of its purpose and clinical positioning, which are different from those of the approved human (autologous) corneal limbus-derived corneal epithelial cell sheets and human (autologous) oral mucosa-derived epithelial cell sheets that are intended for the reconstruction or restoration of the cornea in the eye affected by LSCD.
- The results of Study 170901 does not necessarily indicate Sakracy’s ability to maintain the adhesion-free state, and “release of adhesion” should be changed to “alleviation of adhesion” or the like.

Based on the above comments raised from the expert advisors, PMDA requested the applicant to modify the “Indication or Performance” of Sakracy as shown below. The applicant responded appropriately, and PMDA accepted the response.

Indication or Performance

Alleviation of adhesions on the ocular surface accompanying limbal stem cell deficiency

1.4 Dosage and administration or method of use

As a result of the review in Section “7.R.6 Dosage and administration or method of use” of the Review Report (1), PMDA has concluded that the “Dosage and Administration or Method of Use” of Sakracy should be described as in the mentioned section of the Review Report (1). In addition, PMDA concluded that “Indications” of the immunosuppressants (cyclosporine and cyclophosphamide) used after the treatment with Sakracy be modified by adding a statement of “suppression of immunoreactions induced by cell transplantation” and “Dosage and Administration” note that “use in accordance with the dosage and administration or method of use of the regenerative medical product.”

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion, and PMDA requested the applicant to modify the “Dosage and Administration or Method of Use” of Sakracy as shown below. The applicant responded appropriately, and PMDA accepted it.

Dosage and Administration or Method of Use

1. Production of cell sheet

Pieces of the oral mucosal tissue, 6 mm in diameter, are collected from 2 to 4 sites of the patient’s intraoral buccal mucosa confirmed to be lesion- or inflammation-free. The collected oral mucosal tissue is delivered to the manufacturer using the oral mucosal tissue transport set.

2. Transplantation of cell sheet

Ocular surface adhesion is released, and conjunctival scar tissue is removed from the ocular surface wherever possible. The oral mucosal epithelial cell sheet is transplanted on the exposed ocular surface by a suture technique. The oral mucosal epithelial cell sheet may be cut into pieces to be transplanted on the non-corneal areas, depending on the degree and range of the adhesion. For an exposed ocular surface larger than the oral mucosal epithelial cell sheet, the transplantation of the oral mucosal epithelial cell sheet is preceded by amniotic membrane transplantation.

3. Post-transplant treatments

The following treatments are provided where necessary.

- Use of a therapeutic contact lens
- For patients with a primary disease other than OCP, oral cyclosporine 2 to 3 mg/kg daily from the day after transplantation, with dose adjustment according to the symptoms
- For patients with a primary disease of OCP, oral cyclosporine 2 to 3 mg/kg daily and oral cyclophosphamide 50 mg (on the anhydrous basis) once daily from the day after transplantation, with dose adjustment according to the symptoms

1.5 Post-marketing surveillance plan (draft)

In the present application, the applicant proposed a plan of post-marketing surveillance covering all patients treated with Sakracy to evaluate the safety and efficacy of the product in post-marketing clinical setting. The safety specification is all adverse events associated with the use of Sakracy; the planned sample size is 200 patients per year; and the observation period is from the tissue collection for the production of Sakracy to Week 24 post-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 the proposed post-marketing surveillance plan is acceptable.

The following comments were raised from the expert advisors at the Expert Discussion. PMDA’s conclusions on the other issues were supported.

- For the following reasons, the observation period should be extended to Week 52 post-transplant, and safety and efficacy information should be collected throughout the period: experience with Sakracy is extremely limited; (b) the treatment with Sakracy may be followed by secondary procedures such as corneal transplantation; and (c) the treatment of LSCD-associated adhesion requires a long-term follow-up depending on the primary disease.

- Given that Sakracy is intended for patients with LSCD accompanied by ocular surface adhesion, the proposed planned sample size is questionable.

Based on the above comments raised from the expert advisors, PMDA requested the applicant to reconsider the observation period and planned sample size. The applicant made the following modifications and submitted the post-marketing surveillance plan shown in Table 21. PMDA accepted.

- The observation period has been extended to Week 52 post-transplant.
- In view of the number of patients with LSCD accompanied by ocular surface adhesion, etc., the number of potential users of Sakracy has been reconsidered. The planned sample size has been corrected to approximately 48 patients per year.

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

Objective	Evaluation of safety and efficacy of Sakracy
Survey method	All-case surveillance
Study population	Patients with adhesion accompanying LSCD
Observation period	From the tissue collection for manufacture of Sakracy to Week 52 post-transplant
Planned sample size	Approximately 48 patients per year
Main survey items	Safety All adverse events associated with the use of Sakracy Efficacy Adhesion score, corrected visual acuity

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 PFSB/MDRMPE Notification No. 1105-2 dated November 5, 2014, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, and by the Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare), PMDA has concluded that Sakracy should be designated as a specified regenerative medical product because the product is prepared using autologous tissue-derived cells and an amniotic membrane substrate derived from an allogeneic biological material, from which infectious risk factors can hardly be eliminated even through viral safety control by donor screening.

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 compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. The inspection and assessment confirmed that the application data were collected and compiled generally in accordance with data integrity standards for the product application. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. Meanwhile, the following finding was noted in Evaluation data 7-1. Although the matter did not significantly affect the overall evaluation of the study, it was notified to the applicant as a finding requiring corrective actions.

Finding requiring corrective actions

Sponsor-investigator

- The written procedure for deliberation at the Efficacy and Safety Evaluation Committee was not appropriately documented.

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

The new regenerative medical product application data (Evaluation data 7-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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 the dosage and administrations 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

Alleviation of adhesions on the ocular surface accompanying limbal stem cell deficiency

Dosage and Administration or Method of Use

1. Production of cell sheet

Pieces of the oral mucosal tissue, 6 mm in diameter, are collected from 2 to 4 sites of the patient's intraoral buccal mucosa confirmed to be lesion- or inflammation-free. The collected oral mucosal tissue is delivered to the manufacturer using the oral mucosal tissue transport set.

2. Transplantation of cell sheet

Ocular surface adhesion is released, and conjunctival scar tissue is removed from the ocular surface wherever possible. The oral mucosal epithelial cell sheet is transplanted on the exposed ocular surface by a suture technique. The oral mucosal epithelial cell sheet may be cut into pieces to be transplanted on the non-corneal areas, depending on the degree and range of the adhesion. For an exposed ocular surface larger than the oral mucosal epithelial cell sheet, the transplantation of the oral mucosal epithelial cell sheet is preceded by an amniotic membrane transplantation.

3. Post-transplant treatments

The following treatments are provided where necessary:

- Use of a therapeutic contact lens
- For patients with a primary disease other than ocular cicatricial pemphigoid, oral cyclosporine 2 to 3 mg/kg daily from the day after transplantation, with dose adjustment according to the symptoms

- For patients with a primary disease of ocular cicatricial pemphigoid, oral cyclosporine 2 to 3 mg/kg daily and oral cyclophosphamide 50 mg (on the anhydrous basis) once daily from the day after transplantation, with dose adjustment according to the symptoms

Approval Conditions

1. The applicant is required to disseminate the guidelines for the proper use of the product jointly prepared with academic societies concerned, hold seminars, and take any other necessary measures to ensure that the product be used by doctors with adequate knowledge and experience in limbal stem cell deficiency who have acquired adequate skills for the procedure and knowledge about complications associated with the procedure, at medical institutions with an established medical care system for limbal stem cell deficiency, and in compliance with the “Indication or Performance” and “Dosage and Administration or Method of Use”.
2. Because of a limited number of participants in the clinical studies, the applicant is required to conduct a drug use-results survey covering all patients treated with the product, in principle, until the end of the re-examination period, to understand the characteristics of patients treated with the product and promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

List of Abbreviations

Application	Application for marketing approval
BSA	Bovine serum albumin
CI	Confidence interval
Cyclophosphamide	Cyclophosphamide hydrate
FAS	Full analysis set
GVHD	Graft versus host disease
HBV	Hepatitis B virus
HCL	Hard Contact Lens
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HTLV	Human T-cell leukemia virus
logMAR	Logarithmic minimum angle of resolution
LSCD	Limbal stem cell deficiency
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MMC	Mitomycin C
NEI VFQ-25	The 25-item National Eye Institute Visual Function Questionnaire
OCP	Ocular cicatricial pemphigoid
PMDA	Pharmaceuticals and Medical Devices Agency
POV	Paliades of Vogt
PVB19	Parvovirus B19
QOL	Quality of life
Sakracy	Sakracy
SCL	Soft Contact Lens
SJS	Stevens-Johnson syndrome
Study 170901	Study CQARD-OOS-170901