February 13, 2023
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Human Cellular/Tissue-based Products 1. Human Somatic Cell-processed Product
Non-proprietary Name	Melanocyte-containing Human (Autologous) Epidermis-derived Cell Sheet
Brand Name	JACEMIN
Applicant	Japan Tissue Engineering Co., Ltd.
Date of Application	April 27, 2022 (Application for marketing approval)

Results of Deliberation

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

The product may be approved. The conditional and time-limited approval is not applicable to the product. The re-examination period is 8 years.

The following approval conditions must be satisfied.

Approval Conditions

1. Because the number of patients participating in the clinical trial is very limited, the applicant is required to conduct a use-results survey covering all patients treated with the product, in principle, until the end of the re-examination period, in order to identify the characteristics of patients using the product and promptly collect safety and efficacy data of the product, thereby taking necessary measures to ensure the proper use of the product.
2. Taking account of the risk associated with heterologous transplantation of murine embryonic 3T3-J2 cells used as the feeder cells during the manufacturing process of the product, the applicant is required to take necessary measures, such as storage of the final product samples and retention of use records for 30 years to ensure the proper handling 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

February 1, 2023
Pharmaceuticals and Medical Devices Agency

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

Brand Name	JACEMIN
Classification	Human Cellular/Tissue-based Products 1. Human Somatic Cell-processed Product
Non-proprietary Name	Melanocyte-containing Human (Autologous) Epidermis-derived Cell Sheet
Applicant	Japan Tissue Engineering Co., Ltd.
Date of Application	April 27, 2022

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medicine product consisting of cultured epidermis package containing an epidermal cell sheet, the primary component, and a tissue transport set, the secondary component. The primary component is a cultured epidermis package containing an epidermal cell sheet (containing melanocytes) prepared by sheet-form cultivation of cells isolated from skin tissue harvested from the patient. The secondary component is a tissue transport set for transporting the skin tissue harvested at a medical institution, consisting of tissue transport tubes.

Application Classification	(1-1) New regenerative medical product
Items Warranting Special Mention	None
Reviewing Office	Office of Cellular and Tissue-based Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of vitiligo for which nonsurgical treatment is ineffective or not indicated, 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.

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.

Indication or Performance

Vitiligo for which nonsurgical treatment is ineffective or not indicated

Dosage and Administration or Method of Use

Operations before the manufacture of epidermal cell sheet

Normal skin tissue (all-layer skin containing dermis and not containing the lesion) of the patient is harvested according to the transplantation plan. The harvested skin tissue should be ≥1 cm^2 in size and spindle-shaped for easy suturing. The normal skin tissue thus harvested is placed in a tissue transport tube, immersed in the transport medium, and transported to the manufacturer.

Operations in epidermal cell sheet transplantation

The epidermis at the target site of the epidermal cell sheet transplantation is abraded. The epidermal cell sheet is transplanted onto the abraded site.

Approval Conditions

1. Because the number of patients participating in the clinical trial is very limited, the applicant is required to conduct a use-results survey covering all patients treated with the product, in principle, until the end of the re-examination period, in order to identify the characteristics of patients using the product and promptly collect safety and efficacy data of the product, thereby taking necessary measures to ensure the proper use of the product.
2. Taking account of the risk associated with heterologous transplantation of murine embryonic 3T3-J2 cells used as the feeder cells during the manufacturing process of the product, the applicant is required to take necessary measures such as storage of the final product samples and retention of use records for 30 years to ensure the proper handling of the product.

Attachment

Review Report (1)

December 9, 2022

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

Product Submitted for Approval

Brand Name	JACEMIN
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The product is a regenerative medicine product consisting of cultured epidermis package containing an epidermal cell sheet, the primary component, and a tissue transport set, the secondary component. The primary component is a cultured epidermis package containing an epidermal cell sheet (containing melanocytes) prepared by sheet-form cultivation of cells isolated from skin tissue harvested from the patient. The secondary component is a tissue transport set for transporting the skin tissue harvested at a medical institution, consisting of tissue transport tubes.

Proposed Indication or Performance

Stable vitiligo (vitiligo vulgaris or piebaldism)

Proposed Dosage and Administration or Method of Use

Operations before the manufacture of epidermal cell sheet

Normal skin tissue (not containing the lesion) of the patient is harvested. The harvested skin tissue is $\geq$1 cm^2 in size as a guide, and the area of the skin harvested varies depending on the number of the sheets required for transplantation. The harvested skin should be whole-layer skin containing the dermis and spindle-shaped for easy suturing. The normal skin tissue thus harvested is placed in a tissue transport tube, immersed in the transport medium, and transported to the manufacturer.

Operations in epidermal cell sheet transplantation

The epidermis at the target site of the epidermal cell sheet transplantation is abraded by CO_2 laser, a grinder, etc. The epidermal cell sheet is transplanted onto the abraded site. The transplant site is protected by a suitable wound dressing material and immobilized using a plaster cast or Schiene, as necessary.

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

JACEMIN is a combination product comprising the following 2 components:
Primary component: A green-type human (autologous) epidermis-derived cell sheet which is generated from a skin section in a sheet form by cultivation and growth of the epidermal cells under conditions where melanocytes are maintained. The skin section (not containing the lesion site) is harvested from the patient.
Secondary component: A tube (containing tissue-transport medium) for transporting the skin tissue harvested from the patient to the manufacturing site

JACEMIN is a regenerative medicine product that is applied to the site of stable vitiligo (with missing or reduced melanocytes) after abrasion of the epidermal layer, aimed at repigmentation by the supply of epidermal cells including melanocytes.

1.2 Development history etc.

Vitiligo vulgaris and piebaldism are known as main diseases causing stable vitiligo with missing or reduced melanocytes. Vitiligo vulgaris is caused by posteriori melanocyte degradation resulting in cessation or reduction in melanin formation, leading to skin depigmentation. Piebaldism is vitiligo caused by autosomal dominant inheritance. Vitiligo affects the appearance of the patients, causing mental strain depending on the site of the occurrence, thereby raising clinical problems such as decreased quality of life (QOL) and interference with social activities.

Stable vitiligo which does not show changes in the disease conditions for a long period is an intractable disease resistant to non-surgical treatments such as topical steroids and phototherapy. Surgical treatments such as skin grafting are currently available options. Main surgical treatments practiced in Japan include split-thickness skin grafting, suction blistering, and punctate full-thickness grafting, all of which are autologous skin grafting, and the following problems are raised: (1) Adverse events occur both at the sites of skin harvesting and skin grafting, and (2) only a limited area is available for a single treatment, necessitating multiple grafting. A novel treatment option is thus desired.

JACEMIN was developed in Japan by the applicant based on the licensed manufacturing process for melanocyte-containing Green type autologous cultured epidermis developed by Michele De Luca, et. al (*Arch Dermatol.* 2000;136:1380-9, *Arch Dermatol.* 2003;139:1303-10, etc.). The manufacturing process was optimized to maintain melanocytes within the epidermal cell sheet based on the manufacturing process of JACE, the approved human (autologous) epidermis-derived cell sheet. The applicant conducted a Japanese phase III study (Study J-TEC-ACE02 [Study ACE02]) in patients with stable vitiligo and, recently submitted for marketing approval of JACEMIN with the results of Study ACE02 as the pivotal data.

As of November 2022, JACEMIN has not been approved or marketed in any country or region.

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

The primary component of JACEMIN is a cultured epidermis package consisting of a melanocyte-containing epidermal cell sheet manufactured by cultivation of cells isolated from the normal skin tissue harvested from the patient in a sheet form. The secondary component is a tissue transport set for transporting the skin tissue harvested at a medical institution, consisting of tissue transport tubes.

2.1 Manufacturing process

2.1.1 Manufacturing process

The manufacturing process of JACEMIN consists of manufacture of the cultured epidermis package, the primary component, and manufacture of the secondary component.

2.1.1.1 Manufacturing process for primary component

The manufacturing process for the cultured epidermis package, the primary component, consists of manufacture of feeder cells and manufacture of epidermal cell sheet.

2.1.1.1.1 Preparation and control of 3T3-J2 cells

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

Characterization and a purity test were performed on the MCB, WCB, and cells cultivated beyond the upper limit of passage generations or cells at the limited of in vitro cell age (CAL) from the step of MCB thawing and seeding in accordance with ICH Q5A (R1) guideline (Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin) and Q5D guideline (Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products). Table 1 shows tests performed for adventitious agents. Results from these tests demonstrated the genetic stability throughout the manufacturing period, and neither viral nor non-viral adventitious agents were detected within the range of tests conducted.

MCB, MWCB, and WCB are stored at ≤−[redacted]°C. No new MCB will be prepared, while new MWCB and WCB will be prepared as necessary.

Table 1. Tests for adventitious agents

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

2.1.1.1.2 Manufacturing process of feeder cells

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

[redacted] is identified as the critical step.

2.1.1.1.3 Manufacturing process of epidermal cell sheet

The manufacturing process of epidermal cell sheet consists of processes for receipt of the skin tissue harvested, [redacted], primary packaging/labeling, test, and packing/shipping.

Critical steps include processes for [redacted].

2.1.1.2 Manufacturing process of tissue transport set

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

2.1.2 In-process control tests

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

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

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

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

Table 3. In-process control tests in the manufacturing process of the cultured epidermis package

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

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

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

Process	Test item
[redacted]	[redacted]
	Sterility test

2.2 Safety evaluation of adventitious agents

2.2.1 Skin tissue

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

2.2.2 Biological ingredients other than skin tissue

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

2.3 Manufacturing process development (comparability)

The following are main changes from the manufacturing process of the cultured epidermis package and the tissue transport set at the Study ACE02 (process for clinical study) to the proposed commercial process:

- Preparation method of [redacted]
- Change in [redacted]
- Change in the method for conducting [redacted]
- Change in [redacted]
- Change in [redacted]

All of the changes were subjected to comparability evaluation on the quality attributes and demonstrated to be comparable between the pre- and post-change products.

2.4 Characterization

The cultured epidermis package was subjected to characterization shown in Table 5.

Table 5. Characterization items

Cell content rate*1	[redacted]
Histological analysis*2	Confirmation of [redacted]
Cell viability*3	[redacted]
Viable cell density*2,*3	[redacted]
Cytokine secretion*3	[redacted]
Colony formation assay*2,*3	[redacted]
[redacted] test*2,*3	[redacted]

*1 Conducted in [redacted].
*2 Conducted in [redacted].
*3 Conducted in [redacted].

2.5 Evaluation of manufacturing process

2.5.1 Removal of process-related impurities

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

Benzylpenicillin potassium, streptomycin sulfate, amphotericin B, kanamycin sulfate, and Impurity A are unlikely to raise safety concerns in humans based on the measured residual values in the final product or [redacted] calculated from the estimated residual values. Therefore, control items for these impurities have not been specified. Impurities of animal origins (residues of bovine serum and feeder cells) are controlled by the specifications for the product (residual bovine serum albumin and residual rate of feeder cells).

2.5.2 Verification

The quality attributes required for JACEMIN include tissue code, cell viability, viable cell density, [redacted], general toxicity, tumorigenicity, bacterial/fungal contamination, presence/absence of endotoxins, mycoplasma contamination, foreign matter contamination, viral infection, residual bovine serum albumin, residual rate of feeder cells, residual antibacterial agents, residual Impurity A, and stability in transport.

Although causes of process variability have not been clearly identified currently in the manufacturing process of the primary component, the quality control strategies based on the verification methods comprising of the following items are constructed, taking account of the quality risks that may arise due to variations in the quality attributes of the skin tissue in order to ensure the target quality attributes for each manufacturing process.

- Manufacturing process parameters and test items shown in Table 6
- In-process control tests (Table 3)
- Specifications for the primary component (Table 7)
- Confirmatory test (Sterility Test [membrane filtration method] in the Japanese Pharmacopoeia)

Table 6. Manufacturing process parameters and tests identified as verification items

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

* Results obtained in the in-process control test conducted on [redacted] are used for [redacted].

2.6 Control of JACEMIN

Tables 7 and 8 show the specifications for the cultured epidermis package and the tissue transport set. Because of the limited shelf-life (60 hours) of the primary component [see Section 3], [redacted] days before the release is used for the test of viable microbial cell count. In addition to the specifications, the sterility confirmatory test (Sterility Test [membrane filtration method] in the Japanese Pharmacopoeia) is conducted using [redacted] collected at the release. Results of the confirmatory test are available after transplantation in the patient.

Table 7. Specifications for cultured epidermis package

Test item	Test method
Package	Visual inspection
Viable cell density	[redacted]
Cell viability	[redacted]
Percentage of epithelial cells	Immunostaining [redacted]
Melanocyte [redacted]	[redacted]
Percentage of residual feeder cells	Immunostaining [redacted]
Residual bovine serum albumin	ELISA
Viable bacteria count*	Microbial Limit test, Total Viable Aerobic Count tests (Japanese Pharmacopoeia)
Mycoplasma test	Nucleic-acid Amplification test (Japanese Pharmacopoeia General Information)
Bacterial endotoxin test	Gel-clot techniques or turbidimetric technique (Japanese Pharmacopoeia)
Physical property testing	• [redacted] • [redacted] • [redacted]

* [redacted] days before the release is used.

Table 8. Specifications for tissue transport set

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

2.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA concluded that the quality of JACEMIN was controlled adequately.

3. Stability and Outline of the Review Conducted by PMDA

3.1 Stability of the primary component

Table 9 shows the outline of the stability studies of the cultured epidermis package.

Table 9. Stability studies of cultured epidermis package

Number of batches	Manufacturing process	Storage condition	Study period	Storage form
4	Process for clinical study*	10°C [redacted]°C [redacted]°C 25°C	60 or [redacted] hours	Primary container (polyethylene terephthalate container [lid, bottom], [redacted] carrier, [redacted] cover sheet, and [redacted] top film)
4		[redacted]°C [redacted]°C [redacted]°C [redacted]°C [redacted]°C [redacted]°C	[redacted] hours	

* [redacted] top film was used for the proposed product, whereas [redacted] top film was used for the product subjected to the stability study.

In the stability studies, no significant changes were observed in the quality attributes when samples were stored at 10°C to 25°C for 60 hours, at [redacted]°C to [redacted]°C for [redacted] hours, or at [redacted]°C to [redacted]°C for [redacted] hours. After storage at [redacted]°C for [redacted] hours, 1 batch did not meet the release criteria for [redacted]. After storage at [redacted]°C for [redacted] hours, all batches failed to meet the acceptance criteria for [redacted] of a cell sheet and 1 batch failed to meet the specifications for [redacted]. After storage at [redacted]°C for [redacted] hours, 1 batch failed to meet the acceptance criteria for [redacted] of the cell sheet. After storage at [redacted]°C for [redacted] hours, 1 batch failed to meet the acceptance criteria for [redacted] and 1 batch failed to meet the acceptance criteria for [redacted] of the cell sheet.

Although the material, etc., of the top film of the test samples used for the stability studies differ between the product for the clinical study and the proposed product, [redacted] of [redacted] was confirmed for ≥60 hours even after the change of the top film.

On the basis of the above, a shelf-life of 60 hours has been proposed for the primary component when stored at 10°C to 25°C using a polyethylene terephthalate container (lid, bottom), [redacted] carrier, [redacted] cover sheet, and [redacted] top film.

3.2 Stability of secondary component

Table 10 shows the outline of the stability study for the tissue transport set.

Table 10. Stability study of tissue transport set

Number of batches	Storage condition	Study period	Storage form
1	2°C or 25°C	[redacted] hours*	Polypropylene container with polyethylene cap

* Sterility test was conducted after storage for [redacted] hours. [redacted] was conducted at the time point of the sterility test, and [redacted] confirmation test was conducted at ≥[redacted] hours after the sterility test.

The stability study demonstrated that the secondary component met the sterility test after storage for [redacted] hours both at 2°C and at 25°C. Accordingly, a shelf-life of 96 hours [redacted] has been proposed for the secondary component when stored at 2°C to 25°C in a polypropylene container with a polyethylene cap. Also, [redacted] was confirmed when the secondary component was stored [redacted] both at 2°C and at 25°C.

3.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA accepted the proposed storage condition and the shelf-life of the primary component and the secondary component.

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

The applicant submitted the results of the *in vitro* study and the results of melanocyte evaluation at the graft recipient site in the clinical study (Study ACE02) as data relating to the primary pharmacodynamics or performance of JACEMIN.

4.1 [redacted] study (Attached document 2-11)

[redacted] study was conducted for *in vitro* characterization to evaluate [redacted] and melanocyte [redacted].

JACEMIN [redacted] was subjected to evaluation of [redacted]. [redacted] was [redacted]% in all [redacted] samples derived from different donors. Melanocyte [redacted] of [redacted] was evaluated. Results showed a higher [redacted] in all batches tested compared with melanocyte [redacted] conducted as the release test for the final product (Table 11).

Table 11. Melanocyte [redacted] in final product and in [redacted] study

	Melanocyte [redacted]
[redacted]	

1) [redacted]

4.2 Evaluation of melanocytes in the skin of grafted area in Study ACE02 (Attached document 7-1)

In Study ACE02 (Attached document 7-1) in patients with stable vitiligo (vitiligo vulgaris or piebaldism), the epidermal layer of the vitiliginous skin was abraded, followed by transplantation of JACEMIN and, in patients who underwent the pathological test, melanocyte count and melanin production in the basal lamina of the grafted area were evaluated on the day of the tissue harvesting and at Week 52 after JACEMIN transplantation. Table 12 shows the changes in melanocyte count and melanin production at Week 52 after JACEMIN transplantation, compared with those on the day of tissue harvesting.

Table 12. Changes in melanocyte count and melanin production in basal lamina (assessment by central review committee)

	No. of subjects receiving pathological test*	Increased	Unchanged	Decreased
Melanocytes	11	8 (72.7%)	3 (27.3%)	0 (0.0%)
Melanin production	11	8 (72.7%)	3 (27.3%)	0 (0.0%)

* Number of subjects who consented and underwent a pathological test both on the day of tissue harvesting and at Week 52 after JACEMIN transplantation.

4.R Outline of the review conducted by PMDA

The applicant's explanation for not submitting *in vivo* study results using animals as data relating to the primary pharmacodynamics or performance of JACEMIN:

The applicant attempted to prepare sheets of epidermal cells of pigmented animal origin but, because of the low proliferative potency of melanocytes precluding the maintenance of melanocytes in the final product, failed to establish an *in vivo* test system to assess the efficacy of JACEMIN. The applicant also attempted to establish an *in vivo* test system wherein epidermal cell sheets of human origin are transplanted to immunocompromised animals. However, because hair follicles of mice skin infiltrate deep into the dermis, allowing rapid spontaneous cure by epidermal cells of hair follicle origin, it was impossible to engraft epidermal cells or melanocytes of human origin to nude mice.

The applicant's explanation about the performance of JACEMIN:

After the transplantation of JACEMIN to the epidermis-abraded area of the skin, epithelialization is considered to occur according to the following mechanism: Immediately after the transplantation, the epidermal cells (the primary component of JACEMIN) attach to the abraded surface and adhere to the dermal layer, and after repeating cell growth and binding to the dermal layer, eventually covering the entire abraded surface.

Melanocyte [redacted] for [redacted] in [redacted] study using JACEMIN [redacted], it was shown that JACEMIN contains melanocytes with proliferative potency. The subjects in Study ACE02 were patients with stable vitiligo (vitiligo vulgaris or piebaldism) with missing or reduced melanocytes. Also, migration of melanocytes from normal tissue does not occur in stable vitiligo [see Section 7.R.2.1]. Thus, melanocytes detected in the grafted area at Week 52 after JACEMIN transplantation in Study ACE02 are considered to be derived from JACEMIN.

These results showed that transplantation of JACEMIN to the area of vitiligo after abrasion of the epidermal layer is expected to lead to engraftment and proliferation of melanocytes contained in JACEMIN, resulting in repigmentation in the vitiliginous area.

PMDA concluded that the explanation of the applicant on the performance of JACEMIN is understandable to a certain extent.

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

The applicant's explanation:

On the basis of the information obtained from the transplantation study in nude mice (Attached document 6-4) and Study ACE02 in patients with stable vitiligo (vitiligo vulgaris or piebaldism) in which the epidermal layer of vitiliginous area was abraded, followed by transplantation of JACEMIN (Attached document 7-1), in the transplantation study using nude mice, cell suspension was injected subcutaneously to facilitate the dispersion to the whole body. In order to investigate the migration of JACEMIN from the transplant site, animals were necropsied on 21 days after the subcutaneous transplantation, and lymphocytes and lung were subjected to Fontana-Masson stain, a method for staining melanin. Fontana-Masson stain-positive cells were detected in the axillary lymph nodes, but results of Berlin blue staining confirmed that the stain was blood absorption image instead of JACEMIN-derived melanin. Therefore, grafted cells are extremely unlikely to be widely distributed in the body.

In Study ACE02, the percentage of subjects showing complete epithelialization at the recipient site reached 100% at Week 26 after JACEMIN transplantation, and it was confirmed that the epithelialization was maintained up to Week 52, suggesting the successful engraftment of JACEMIN-derived epidermal cells. Moreover, the pathological test at Week 52 after transplantation confirmed melanocytes in the skin at the grafted area [see Section 4.2]. These results suggest that JACEMIN-derived epidermal cells and melanocytes survive at the transplant site for ≥52 weeks after transplantation.

5.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the applicant's explanation about the biological disposition of JACEMIN is acceptable.

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

The applicant submitted the following data relating to the nonclinical safety of JACEMIN: Karyology test, soft agar colony formation assay, tumorigenicity studies in nude mice, etc.

6.1 General toxicity

The applicant's explanation:

Although no general toxicity study was conducted, JACEMIN is free from safety problem, judging from the following:

- JACEMIN is applied clinically to the abraded skin surface. Cells in the transplanted JACEMIN are extremely unlikely to be distributed in the whole body.

- In the use-results survey and the post-marketing clinical study of JACE in patients with severe thermal burn, JACE was transplanted to 359 and 29 patients, respectively, and no particular safety problems have been reported in these patients.
- Each sheet of JACEMIN produced approximately 0.20 ng/day of cytokine (IL-6). Although no IL-6 production was detected with JACE, exposure to IL-6 due to JACEMIN is considered to be extremely low with negligible safety concerns, given the fact that IL-6 is diluted by approximately [redacted] ten-thousand-fold during the rinsing process before the release, together with the IL-6 concentration in normal human blood.
- In a tumorigenicity study administering JACEMIN subcutaneously to nude mice, shrinkage of the subcutaneous nodule was observed [see Section 6.2.1.3]. Distribution of JACEMIN to areas other than the transplant site was not observed [see Section 5].

6.2 Other safety

6.2.1 Tumorigenicity study

Karyology tests [Section 6.2.1.1] using [redacted]-passaged cells[2)] (PNGY-P[redacted], ZKOF-P[redacted], and CIOI-P[redacted]) derived from 3 subjects (PNGY, ZKOF, and CIOI), a soft agar colony formation assay [Section 6.2.1.2], and a tumorigenicity study using nude mice [Section 6.2.1.3]) were conducted. The applicant considers that cells constituting JACEMIN have no tumorigenicity, determining from the results of these studies.

6.2.1.1 Karyology test (Attached documents 6-1 and 6-2)

Karyotyping was conducted on [redacted]-passaged cells[3)] (PNGY-P[redacted], ZKOF-P[redacted], and CIOI-P[redacted]) and [redacted]-passaged cells[2)] (PNGY-P[redacted], ZKOF-P[redacted], and CIOI-P[redacted]) derived from 3 subjects (PNGY, ZKOF, and CIOI). No abnormal findings were observed in PNGY-P[redacted] and PNGY-P[redacted] or ZKOF-P[redacted] and ZKOF-P[redacted]. No abnormal findings were observed in CIOI-P[redacted], whereas translocation between the short arm (p13) of chromosome 10 and the long arm (q13) of chromosome 12 as the breakpoints was observed in 3 of 20 CIOI-P[redacted] cells.

In order to confirm the cytogenetic stability of CIOI-P[redacted] with chromosomal abnormality, CIOI-P[redacted] cells were further passaged [redacted] times and subjected to karyotyping. Results showed no increase in cells with reciprocal translocation observed with CIOI-P[redacted] cells. The applicant explained that the results suggested that the cells with said mutation had no proliferative capacity.

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

A soft agar colony formation assay was performed on 3 batches (PNGY-P[redacted], ZKOF-P[redacted], and CIOI-P[redacted]) of [redacted]-passaged cells.[2)] No anchorage-independent cell growth was observed.

6.2.1.3 Transplantation study in nude mice (Attached document 6-4)

Three batches of [redacted]-passaged 1×10^7 cells[2)] (PNGY-P[redacted], ZKOF-P[redacted], and CIOI-P[redacted]) were administered subcutaneously to female nude mice (n = 10/batch), and animals were necropsied on Day 21 after administration. Animals were subjected to monitoring of clinical signs, body weight measurement,

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2) Cells (P[redacted]) [redacted] after [redacted] passaging, as was the case with JACEMIN
3) Cells (P[redacted]) that were passaged [redacted] times

subcutaneous nodule, necropsy, macroscopic observation, and histopathological test (administration site, axillary and inguinal lymph nodes, lung, brain, spleen, liver, and kidney).

No abnormality was observed in clinical signs or body weight during the study period. Subcutaneous nodules regressed on Day 21 as compared to Day 3 after transplantation. Necropsy showed subcutaneous nodules in all animals but did not show growth of JACEMIN-derived cells or atypia.

6.2.2 Safety evaluation of excipients, secondary component, and process-related impurities

The applicant evaluated the safety of excipients, secondary component, and process-related impurities of JACEMIN as shown below, and determined that they pose no significant safety concerns.

The excipients of JACEMIN are Dulbecco's Modified Eagle Medium without phenol red and L-glutamine, neither of which is cytotoxic nor poses safety concerns on the local skin.

Process-related impurities derived from raw materials, etc., are bovine serum (fetal bovine serum, calf serum, and bovine serum), feeder cells, Impurity A, and antibiotics (amphotericin B, kanamycin sulfate, benzylpenicillin potassium, and streptomycin sulfate). The applicant explained that these impurities do not pose any safety risk on humans, determining from the safety evaluation based on their residual amount in JACEMIN, published reports, and previous use experiences as excipients.

6.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that JACEMIN has no particular problem in clinical use from a toxicological point of view.

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

The applicant submitted the evaluation data on the efficacy and safety from a Japanese phase III study shown in Table 13.

Table 13. List of clinical study on efficacy and safety

Data category	Region	Study identifier	Phase	Study population	No. of patients enrolled	Outline of dosage regimen	Main endpoints
Evaluation	Japan	J-TEC-ACE02	III	Patients with stable vitiligo (vitiligo vulgaris or piebaldism)	25	The epidermal layer of vitiligous area was abraded and JACEMIN was transplanted.	Efficacy Safety

7.1 Japanese phase III study (Study ACE02) (Attached document 7-1, Study ACE02 [October 1, 2018 to [redacted], 20[redacted]])

An open-label, uncontrolled, Japanese phase III study was conducted to evaluate the efficacy and safety of JACEMIN in patients with stable vitiligo[4)] (vitiligo vulgaris or piebaldism) (target sample size, 25

4) Vitiligo showing neither expansion nor regression for ≥12 months. Vitiligo vulgaris that does not show regression after treatment with conventional nonsurgical therapy for ≥6 months.

patients[5]) at 7 study sites. In this study, the period from informed consent to tissue harvesting was handled as the "run-in period," the period from tissue harvesting to the first transplantation of JACEMIN as "observation period," and the period after JACEMIN transplantation as "treatment period." Table 14 shows the inclusion/exclusion criteria.

JACEMIN was used according to the procedure described below. In order to avoid the effect on efficacy and safety evaluation, the following treatments were prohibited after JACEMIN transplantation: Phototherapy (psoralen and ultraviolet A [PUVA] therapy, narrow band ultraviolet B (UVB) irradiation, excimer laser/light irradiation), skin grafting, topical steroid, topical active vitamin D3, topical tacrolimus, oral steroid, and oral immunosuppressants.

Normal skin tissue of ≥1 cm^2 was harvested in full thickness from each subject and transplanted onto the surface of vitiligo that had been abraded by CO_2 laser, grinder, etc.

Table 14. Main inclusion/exclusion criteria

Inclusion criteria	1. Patients aged ≥12 years 2. Patients diagnosed with either of the following: (a) Vitiligo vulgaris (b) Piebaldism 3. Patients with vitiligo without expansion or regression for ≥12 months 4. Patients without distinct Koebner's phenomenon for ≥12 months 5. Patients without emergence of new vitiligo for ≥12 months 6. Among patients with vitiligo vulgaris, patients without regression of vitiligo despite treatment with conventional non-surgical therapy (topical therapy with steroid/active vitamin D3/tacrolimus, oral immunosuppressants, and PUVA therapy/narrow band UVB irradiation/excimer laser/light irradiation, etc.) for ≥6 months
Exclusion criteria	1. Patients with autoimmune disease under treatment 2. Patients on systemic administration of corticosteroid 3. Patients with malignant skin tumor, patients with suspected malignant skin tumor, and patients who recovered from malignant skin tumor <5 years ago (among patients with malignant skin tumor, patients with solar keratosis are excluded only if solar keratosis is located at the harvesting site or the recipient site).
Criteria for vitiligo selection for treatment	1. Stable vitiligo without expansion or regression for ≥12 months 2. Continuous vitiligos ≥2 cm^2 and ≤1,200 cm^2 in size 3. Vitiligo on uneven skin surface and vitiligo in joint range of motion are not selected for treatment.

A total of 25 subjects were enrolled in Study ACE02. One of them withdrew informed consent after tissue harvesting and was not subjected to safety monitoring. The remaining 24 subjects who underwent tissue harvesting and JACEMIN transplantation were included in the safety analysis set and the efficacy analysis set. None of the subjects in the safety analysis set or the efficacy analysis set discontinued the study.

Table 15 shows the characteristics of subjects. The size of JACEMIN was 8 × 10 cm (effective area 80 cm^2). The number of sheets transplanted was 3 in 2 subjects, 2 in 5 subjects, and 1 in 17 subjects. Table 16 shows the area of JACEMIN transplantation.

[5] By assuming the primary endpoint "expected repigmentation rate (%) at Week 52 after JACEMIN transplantation" to be 75% with 39% standard deviation (SD), the number of subjects required to conduct hypothesis testing for 50% threshold with two-sided significance level of 5% and statistical power of 80% was calculated to be 22. The target sample size was 25 to allow a drop-out rate of 10%.

Table 15. Characteristics of subjects

No. of subjects		24
Sex	Male	7 (29.2%)
	Female	17 (70.8%)
Age (years)	<20	9 (37.5%)
	≥20	15 (62.5%)
Complication	No	5 (20.8%)
	Yes	19 (79.2%)
Primary disease	Vitiligo vulgaris (non-segmental)	10 (41.7%)
	Vitiligo vulgaris (segmental)	12 (50.0%)
	Piebaldism	2 (8.3%)
Detailed site of vitiligo*	Head and neck (frontal)	18 (75.0%)
	Head and neck (back)	5 (20.8%)
	Trunk	9 (37.5%)
	Shoulder to upper elbow (not including elbow)	2 (8.3%)
	Elbow to fingertip	6 (25.0%)
	Thigh to upper knee (not including knee)	4 (16.7%)
	Knee to toe	6 (25.0%)
Pathological test	No	13 (54.2%)
	Yes	11 (45.8%)
Method for epidermal abrasion	Grinder	0
	CO_2 laser	17 (70.8%)
	Ultrasonic surgical device	2 (8.3%)
	Erbium YAG laser	0
	Hydraulic knife	5 (20.8%)

* Multiple choices included

Table 16. Area of JACEMIN transplantation

Number of subjects		24
JACEMIN transplantation area (cm^2)	Mean	39.03
	SD	50.98
	Median	18.90
	Min, Max	4.7, 212.9
	25 percentile point, 75 percentile point	12.65, 42.20

The primary endpoint was the repigmentation rate[6)] at Week 52 after JACEMIN transplantation. A statistically significant difference was observed from the pre-defined threshold level of 50% ($P = 0.0201$, two-sided significance level of 5%, 1-sample t-test), as shown in Table 17.

Table 17. Results of primary endpoint (efficacy analysis set)

No. of subjects		24
Repigmentation rate (%)	Mean	68.0
	SD	35.3
	Median	86.3
	Min, Max	0, 100.0
	95% CI	53.1-82.9
	P value*	0.0201

* Two-sided significance level of 5%, 1-sample t-test

Tables 18 to 24 show results of the secondary endpoints.

6) The investigator, etc., other than the attending physician attached the colorless and transparent cover over the site of JACEMIN transplantation and traced the area without repigmentation. The sponsor measured the traced area using the image analysis software (Image J) and calculated the repigmentation rate according to the following equation. In order to ensure the objectivity of the repigmentation rate assessment, the independent central review committee assessed the validity of the evaluation by the investigator, etc., based on the photograph of JACEMIN transplant site and the tracing by the investigator, etc. If the assessment was considered "inappropriate," the central review committee identified the site without repigmentation from the photograph of JACEMIN transplant site.

$$\text{Repigmentation rate (\%)} = \frac{\text{Area of JACEMIN transplantation } (cm^2) - \text{Area without repigmentation } (cm^2)}{\text{Area of JACEMIN transplantation } (cm^2)} \times 100$$

Table 18. Changes over time in repigmentation rate (efficacy analysis set)

	Repigmentation rate (%)			
	Week 12 after transplantation	Week 26 after transplantation	Week 39 after transplantation	Week 52 after transplantation
No. of subjects	19	22	22	24
Mean	41.1	59.5	64.5	68.0
SD	40.9	35.9	35.7	35.3
Median	28.7	64.4	77.7	86.3
Min, Max	0, 98.2	0, 100.0	0, 100.0	0, 100.0

Table 19. Changes over time in repigmentation rate by primary disease (efficacy analysis set)

		Repigmentation rate (%)			
		Week 12 after transplantation	Week 26 after transplantation	Week 39 after transplantation	Week 52 after transplantation
Vitiligo vulgaris (non-segmental)	No. of subjects	9	10	10	10
	Mean	35.6	43.7	50.2	55.4
	SD	43.6	38.9	41.3	43.0
	Median	1.6	38.1	49.9	57.0
	Min, Max	0, 94.2	0, 100.0	0, 100.0	0, 100.0
Vitiligo vulgaris (segmental)	No. of subjects	10	11	11	12
	Mean	46.0	72.2	75.3	80.6
	SD	40.1	29.8	27.4	24.5
	Median	45.6	87.4	86.4	93.2
	Min, Max	0, 98.2	12.0, 100.0	23.1, 100.0	26.8, 100.0
Piebaldism	No. of subjects	0	1	1	2
	Mean	—	77.1	88.5	55.4
	SD	—	—	—	39.3
	Median	—	77.1	88.5	55.4
	Min, Max	—	77.1, 77.1	88.5, 88.5	27.6, 83.2

Table 20. Changes over time in the number of subjects by category of repigmentation rate (efficacy analysis set)

Repigmentation rate (%)	Week 12 after transplantation	Week 26 after transplantation	Week 39 after transplantation	Week 52 after transplantation
<50%	10 (52.6%)	9 (40.9%)	7 (31.8%)	6 (25.0%)
≥50% and <75%	2 (10.5%)	2 (9.1%)	2 (9.1%)	4 (16.7%)
≥75%	7 (36.8%)	11 (50.0%)	13 (59.1%)	14 (58.3%)

Table 21. Changes over time in the pattern* of repigmentation (efficacy analysis set)

	Week 12 after transplantation	Week 26 after transplantation	Week 39 after transplantation	Week 52 after transplantation
Uniform	4 (25.0%)	5 (23.8%)	5 (23.8%)	9 (42.9%)
Non-uniform	12 (75.0%)	16 (76.2%)	16 (76.2%)	12 (57.1%)

* The investigator, etc., assessed the uniformity by visual inspection.

Table 22. Changes over time in the extent of color matching* (efficacy analysis set)

	Assessment by investigator, etc.			
	Week 12 after transplantation	Week 26 after transplantation	Week 39 after transplantation	Week 52 after transplantation
Dark	1 (6.3%)	2 (9.5%)	1 (4.8%)	3 (14.3%)
Same	6 (37.5%)	7 (33.3%)	10 (47.6%)	10 (47.6%)
Light	9 (56.3%)	12 (57.1%)	10 (47.6%)	8 (38.1%)
	Assessment by the subject			
	Week 12 after transplantation	Week 26 after transplantation	Week 39 after transplantation	Week 52 after transplantation
Dark	1 (6.3%)	2 (9.5%)	1 (4.8%)	4 (19.0%)
Same	7 (43.8%)	7 (33.3%)	9 (42.9%)	8 (38.1%)
Light	8 (50.0%)	12 (57.1%)	11 (52.4%)	9 (42.9%)

* The investigator and each subject compared the color of the JACEMIN transplant site with the color of the surrounding normal skin by visual inspection, and rated it according to 3 levels: Dark, same, and light.

Table 23. Degree of treatment satisfaction* (efficacy analysis set)

	Assessment by investigator, etc.		Assessment by subject	
	Week 39 after transplantation	Week 52 after transplantation	Week 39 after transplantation	Week 52 after transplantation
Low	5 (20.8%)	5 (20.8%)	5 (20.8%)	7 (29.2%)
Rather low	8 (33.3%)	7 (29.2%)	7 (29.2%)	3 (12.5%)
High	10 (41.7%)	11 (45.8%)	8 (33.3%)	12 (50.0%)
Very high	1 (4.2%)	1 (4.2%)	4 (16.7%)	2 (8.3%)

* The investigator and each subject assessed the degree of satisfaction with JACEMIN therapy according to 4 levels of low, rather low, high, and very high.

Table 24. QOL assessment by the use of Skindex16 (Japanese version) questionnaire* (efficacy analysis set)

No. of subjects		24		
Scale		Screening	Week 39 after transplantation	Week 52 after transplantation
Overall	Mean	18.8	16.8	15.8
	SD	17.5	21.1	18.1
	Median	12.0	9.4	14.6
	Min, Max	1.0, 64.6	0, 74.0	0, 64.6
Symptoms	Mean	5.9	7.3	7.1
	SD	13.4	11.9	10.9
	Median	0	0	0
	Min, Max	0, 50.0	0, 37.5	0, 33.4
Emotions	Mean	29.6	25.0	24.3
	SD	23.8	27.7	25.8
	Median	25.0	15.5	15.5
	Min, Max	0, 85.7	0, 97.6	0, 85.7
Functioning	Mean	13.9	12.8	10.7
	SD	26.5	26.2	23.0
	Median	0	0	0
	Min, Max	0, 86.7	0, 90.0	0, 80.0

* The questionnaire consists of questions on 16 items belonging to 3 subscales of symptoms, emotions, and function. The patient rates the severity of the most bothersome skin symptom during the past 1 week according to 7 scales from “not bothered at all” to “bothered always.” The point is converted to a score of 0 to 100. The higher the score, the lower the QOL.

During the observation period, adverse events were reported in 6 of 24 subjects (25.0%). There were no deaths or serious adverse events. Adverse events observed in ≥2 subjects were procedural pain in 4 subjects.

During the treatment period, adverse events were reported in 23 of 24 subjects (95.8%). No death occurred. The serious adverse event reported was large intestinal polypectomy in 1 subject, but its causal relationship to JACEMIN was denied. Main adverse events were skin erosion in 11 subjects (45.8%),

application site pain in 10 subjects (41.7%), pruritus in 7 subjects (29.2%), and hypertrophic scar in 6 subjects (25.0%).

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA reviewed the efficacy of JACEMIN based on the investigation of the design of Study ACE02 and the efficacy endpoints, taking account of the following:

(1) Study ACE02, data of which were submitted as the evaluation data for the present application, is an open-label, uncontrolled study, and

(2) There is no consensus on indices for efficacy assessment in clinical studies on vitiligo

7.R.2 Efficacy

On the basis of the results of the following review, PMDA concluded that JACEMIN has a certain level of efficacy against stable vitiligo.

7.R.2.1 Design of Study ACE02 and efficacy endpoints

The applicant's explanation about the appropriateness of conducting Study ACE02 as an uncontrolled, open-label study:

- The clinical practice guidelines for vitiligo vulgaris (in Japanese) (*The Japanese Journal of Dermatology.* 2012;122:1725-40) state that surgical treatment of vitiligo vulgaris should be conducted only at cosmetically required sites in patients without disease progression within the past 1 year. Surgical treatments conducted in Japan include split-thickness skin grafting, suction blister grafting, and punctate full thickness skin grafting. All of these methods are autologous skin grafting, and have the following problems: (1) Adverse events occur both at the site of skin harvesting and at the site of skin grafting; and (2) only a limited area is available for each single treatment, necessitating multiple treatments. In addition, since there are no established standard treatment methods including phototherapy conducted as an additional treatment (*Postepy Dermatol Alergol* 2018;35:592-8, *Dermatology* 2021;237:835-42, etc.), it is not appropriate to conduct a conventional surgical treatment as the control therapy.
- Vitiligo under stable state contains diminished or no melanocytes with no melanocyte migration from the surrounding normal tissue (*Pigment Cell Res* 1994;7:193-203), precluding the possibility of a spontaneous cure of vitiligo.
- It is next to impossible to blind the physician and the patient to the information on whether JACEMIN has been transplanted.

The applicant's explanation about inclusion of subjects in the efficacy analysis set:

On the basis of the prespecified criteria, whether each subject should be included was evaluated for all subjects by the case review committee consisting of medical experts and the coordinating investigator. Five subjects who used a topical steroid, a drug prohibited due to the possible effect on efficacy, were included in the efficacy population because the investigator and other committee members considered that the medication had no sufficient add-on effect on efficacy requiring study discontinuation, assessing from the type and duration of the topical steroid used. Also, handling of 13 data in 6 subjects was discussed in the case review committee. All of these data were repigmentation rate and were handled as

shown below: The repigmentation rate [95% confidence interval (CI)] at Week 52 after JACEMIN transplantation was 67.8% [52.7%, 82.9%] before the discussion at the case review committee meeting.

- For 7 cases[7] of "negative repigmentation rate" in 5 subjects, the area with no repigmentation was larger than the grafted area. This was more likely to be caused by (1) error in tracing the grafted area or vitiligous area on the observation day after transplantation, (2) misidentification of the grafted site or error caused by extension of skin, or (3) difference in the body posture at the time of tracing the vitiligo by time of observation. Accordingly, the repigmentation rate was corrected to 0%, the lowest rate.
- For 5 cases[8] of "despite absence of site with repigmentation, the repigmentation rate is not 0%" in 3 subjects, the error in 1 subject was caused by tracing the grafted area or the vitiligous area on the observation day after transplantation and the error due to extension of the skin, possibly due to the error of misidentification of the grafted site. In 2 subjects, there was no site with repigmentation, and the discrepancy was caused by an error in tracing the grafted area or the vitiligous area on the observation day after transplantation. Accordingly, the repigmentation rate in these subjects was corrected to 0%.
- For 1 case[9] of "despite presence of site with repigmentation, the repigmentation rate is 0%" in 1 subject, the area of repigmentation was minimal. In addition, due to an error in tracing the vitiligous area, the grafted area and the traced vitiligous area at Week 39 after JACEMIN transplantation were coincidentally identical values. Accordingly, the repigmentation rate in this subject was considered to be 0% for conservative assessment.

The applicant's explanation about the efficacy endpoints:
The primary efficacy endpoint of vitiligo vulgaris is the repigmentation rate as stated in the consensus at the Vitiligo Global Issues Consensus Conference (*Pigment Cell Melanoma Res.* 2017;30:28-40). In fact, the repigmentation rate was used as the primary endpoint in a majority (43 of 51) of reports described in a systematic review on vitiligo vulgaris (*Br J Dermatol.* 2012;167:804-14), suggesting the appropriateness of using the repigmentation rate as the primary endpoint. Week 52 was considered an appropriate timing of assessment because results of a preceding study (*Ann Plast Surg.* 2004;53:178-80) showed that repigmentation caused by melanocyte-maintaining autologous epidermis transplantation has been stabilized at Week 52 after transplantation.

Also, the 50% threshold for the repigmentation rate is considered to be of clinical significance, taking account of the following:

- In the above systematic review, 28 of 43 reports that used the repigmentation rate as the endpoint evaluated the repigmentation rate of ≥50% as beneficial.
- The repigmentation rate in vitiligo treatment is 67.5% to 76.5% with suction blister grafting combined with phototherapy, etc. (*Postepy Dermatol Alergol.* 2018;35:592-8, *Dermatology.* 2021;237:835-42) and 30.7% to 38.5% with punctate full thickness skin grafting combined with

[7] Registration No. ATA1 (Week 12 after JACEMIN transplantation), registration No. ATB2 (Week 52 after JACEMIN transplantation), registration No. ATC1 (Week 12 after JACEMIN transplantation), registration No. ATE1 (Weeks 26 and 39 after JACEMIN transplantation), and registration No. ATF3 (Weeks 12 and 26 after JACEMIN transplantation)
[8] Registration No. ATB2 (Weeks 12, 26, and 39 after JACEMIN transplantation), registration No. ATE1 (Week 52 after JACEMIN transplantation), and registration No. ATE6 (Week 12 after JACEMIN transplantation)
[9] Registration No. ATA1 (Week 39 after JACEMIN transplantation)

phototherapy, etc. (*J Eur Acad Dermatol Venereol.* 2012;26:690-5, *Clin Cosmet Investig Dermatol.* 2021;14:827-35), suggesting that these surgical treatments alone are unlikely to achieve a repigmentation rate of >50%.

- The degree of treatment satisfaction, assessed by the physician and the subject, was "rather low" or "low" in all 6 subjects with a repigmentation rate of <50% at Week 52 after JACEMIN transplantation. In contrast, among 18 subjects with a repigmentation rate of ≥50% at Week 52 after JACEMIN transplantation, the degree of treatment satisfaction was "rather good" or "good" in 66.7% of them by the assessment of the investigator, etc., and in 77.8% according to the assessment of the subject.

PMDA's view:
The applicant's explanation of conducting Study ACE02 as an open-label, uncontrolled study is acceptable. However, handling of the repigmentation rate in the case review committee meeting should have been specified in advance. Also, assumption of the negative repigmentation rate to be 0% is likely to have caused overestimation of the efficacy of JACEMIN in the primary endpoint analysis. Nevertheless, there was no significant difference in the repigmentation rate at Week 52 after JACEMIN transplantation, between before and after the review at the case review committee meeting. Therefore, it was acceptable to evaluate the efficacy of JACEMIN based on the results after the case review committee meeting on Study ACE02. The applicant's explanation about the handling of subjects who used topical steroid is acceptable, taking account of the fact that the target of Study ACE02 is stable vitiligo.[4)]

Similarly, the applicant's explanation about the primary endpoint in Study ACE02, timing of primary endpoint assessment, and the threshold level specified is acceptable to a certain extent. However, since the objective of vitiligo treatment by JACEMIN transplantation is cosmetic improvement, PMDA decided to evaluate the efficacy of JACEMIN based not only on the repigmentation rate but also on the pattern of repigmentation, extent of color matching, treatment satisfaction, and QOL assessment.

7.R.2.2 Efficacy results

The applicant's explanation about the results of efficacy in Study ACE02:

- In the primary analysis population, the repigmentation rate [95% CI] at Week 52 after JACEMIN transplantation was 68.0% [53.1%, 82.9%], showing a statistically significant difference from the pre-defined threshold level (50%) [see Section 7.1].
- Tables 18, 21, and 22 show changes over time up to Week 52 after JACEMIN transplantation in the repigmentation rate, repigmentation pattern, and extent of color matching. These results suggest that repigmentation progresses gradually as a result of engraftment of melanocytes with proliferative potency contained in JACEMIN at the transplant site. As for the pattern of repigmentation and the extent of color matching, a higher treatment effect will be expected by the combined use of phototherapy, etc., which were prohibited in Study ACE02, according to the wish of the patient.
- At Week 52 after JACEMIN transplantation, the repigmentation rate was >50%, the pattern of repigmentation was "uniform," and the extent of color matching was "equal," in 6 of 24 subjects.

- Table 23 shows the degree of treatment satisfaction, which was rated “good” or “very good” at Week 52 after JACEMIN transplantation in 50.0% (12 of 24) of subjects according to the investigator’s assessment, and 58.3% (14 of 24) of subjects according to the subjects.
- Table 24 shows the results of QOL assessment up to Week 52 after JACEMIN transplantation. The total score (mean ± standard deviation [SD]) of symptoms, emotions, and functioning was 18.8 ± 17.5 at screening and 15.8 ± 18.1 at Week 52 after JACEMIN transplantation.

The applicant’s explanation:
In 6 subjects, although the repigmentation rate at Week 52 after JACEMIN transplantation exceeded 50%, the degree of treatment satisfaction was rated “rather bad” or “bad” by the investigator, etc. for the following reasons:
- In 5 of 6 subjects, the pattern of repigmentation was assessed as “non-uniform” or the extent of color matching as “lighter.”
- In the remaining 1 subject, the repigmentation rate was assessed as 96.2%, repigmentation pattern as “uniform,” and extent of color matching as “equal.” However, because the vitiligo was located at the right temple of the forehead, a prominent part, the level of expectation for treatment was high, together with hypertrophic scar observed.

PMDA’s view:
The objective of vitiligo treatment by JACEMIN transplantation is to achieve cosmetic improvement by replacing the epidermis of the vitiligous area with healthy epidermis containing melanocytes. A statistically significant difference from the threshold value was observed in repigmentation rate at Week 52 after JACEMIN transplantation, the primary endpoint. In addition, based on the results of the secondary endpoints, i.e., pattern of repigmentation, change over time in the extent of color matching, degree of treatment satisfaction, and QOL, JACEMIN demonstrated the efficacy to a certain extent against stable vitiligo.

However, at Week 52 after JACEMIN transplantation monotherapy, only 25.0% (6 of 24) of subjects achieved the repigmentation rate of >50%, uniform repigmentation of the grafted area, and same color matching with the surrounding normal tissue. After the market launch, it is anticipated that phototherapy, topical steroid, etc., treatments that had been prohibited in Study ACE02, are used in combination, depending on the situation of repigmentation and the patient’s wish. Information on the clinical course of patients receiving phototherapy, topical steroid, etc., after JACEMIN transplantation should be collected after the market launch.

7.R.3 Safety

As a result of the following reviews, PMDA considered that the adverse event requiring special attention in JACEMIN transplantation is hypertrophic scar. PMDA concluded that the risk associated with JACEMIN transplantation is acceptable, given the following actions: (1) Provision of appropriate information on adverse events observed in Study ACE02 to healthcare professionals by means of materials, etc. and (2) appropriate measures such as monitoring and controlling of adverse events taken by a physician with sufficient knowledge and experience in the treatment of vitiligo and surgical treatment of skin based on said information.

7.R.3.1 Incidences of adverse events in Study ACE02

The applicant's explanation about the safety of JACEMIN:

Table 25 shows the incidence of adverse events during the observation period and the treatment period of Study ACE02. No death occurred. Large intestinal polypectomy was observed as a serious adverse event during the treatment period, but its causal relationship to JACEMIN or the surgical procedure was denied. Most adverse events occurred at the site of JACEMIN transplantation and are controllable by careful postoperative management.

Table 25. Adverse events observed during the observation period and the treatment period of Study ACE02

	Observation period	Treatment period
All adverse events	6 (25.0)	23 (95.8)
Serious adverse events	0	1 (4.2)
Grade ≥3 adverse events	0	2 (8.3)*1
Adverse events observed in ≥2 subjects		
Skin erosion	0	11 (45.8)
Application site pain	0	10 (41.7)
Pruritus	0	7 (29.2)
Hypertrophic scar	0	6 (25.0)
Gastroenteritis	0	4 (16.7)
Eczema	0	4 (16.7)
Procedural pain	4 (16.7)	0
Nausea	0	2 (8.3)
Stomatitis	0	2 (8.3)
Acne	0	2 (8.3)
Dermatitis contact	0	2 (8.3)
Erythema	0	2 (8.3)
Vitiligo	0	2 (8.3)
Medical device site erythema*2	0	2 (8.3)

Number of subjects with events (incidence [%])
Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) Ver 24.0
*1 Hypertrophic scar and colitis ischaemic in 1 patient each
*2 Erythema caused by abrasion of the surface layer of vitiligous area with CO_2 laser before JACEMIN transplantation

Taking account of hypertrophic scar observed in 6 subjects, including Grade 3 cases, PMDA conducted the following reviews on important risks associated with JACEMIN transplantation, with the emphasis on hypertrophic scar.

7.R.3.2 Individual events

7.R.3.2.1 Hypertrophic scar

The applicant's explanation about hypertrophic scar after JACEMIN transplantation:

Hypertrophic scar occurred in 6 subjects (Grade 1 in 2 subjects, Grade 2 in 3 subjects, Grade 3 in 1 subject) 50 to 279 days after JACEMIN transplantation, and all events were considered to be related to the skin abrasion performed before JACEMIN transplantation. Grade 1 events in 2 subjects resolved without any treatment, whereas 3 subjects with Grade 2 events and 1 subject with Grade 3 event were treated with topical steroid, local steroid injection, tranilast administration, etc., which led to improvement or recovery in all treated subjects. One subject with Grade 3 event (onset of hypertrophic scar on Day 81 after JACEMIN transplantation) received laser therapy in combination with the above drug therapy, and the time from the onset to improvement was 532 days.

Factors of the observation of hypertrophic scar in 25% (6 of 24) of subjects receiving JACEMIN transplantation are following: (1) Hypertrophic scar is a risk associated with surgical treatment of skin and (2) topical steroid was prohibited in Study ACE02, which caused a delay in the use of topical steroid when findings related hypertrophic scar, such as erythema, were noticed. Hypertrophic scar is controllable by adequate and prompt use of topical steroid. Information on the skin abrasion procedure and management after JACEMIN transplantation will be provided to healthcare professionals appropriately by means of materials, etc.

PMDA's view:
Hypertrophic scar (including Grade 3 scar) was observed in 6 of 24 subjects receiving JACEMIN transplantation, which necessitated treatment with laser, etc., and long-term treatment and management due to the delay in onset. Caution is required against hypertrophic scar after JACEMIN transplantation. Information on the incidence of hypertrophic scar in the clinical study and the method for management upon noticing findings related to hypertrophic scar should be provided to healthcare professionals in an appropriate manner in order to raise caution.

7.R.3.2.2 Skin erosion

The applicant's explanation about skin erosion after JACEMIN transplantation:
Skin erosion occurred between Day 7 and Day 86 after JACEMIN transplantation in 11 subjects (Grade 1 in 7 subjects, Grade 2 in 4 subjects). A causal relationship of the event to the surgical technique could not be ruled out in 6 subjects, while in 1 subject, a causal relationship to JACEMIN could not be ruled out. Skin erosion resolved without treatment in 2 subjects with Grade 1 events, while in the remaining 5 subjects with Grade 1 event and in 4 subjects with Grade 2 events, skin erosion resolved after treatment with topical medication and wound dressing material depending on the condition of the wounded area.

Skin erosion is highly likely to be caused by the poor technique of epidermal abrasion, inadequate management of wound after JACEMIN transplantation, or scratching to soothe pruritus associated with wound healing process. The skin erosion is considered to be manageable by topical medication and wound dressing material as are the cases with other conventional surgical treatment of the skin. Information on the skin abrasion procedure and management after JACEMIN transplantation will be provided to healthcare professionals appropriately by means of materials, etc.

PMDA's view:
All of the observed cases of skin erosion were nonserious events. Given the severity grade, time to onset, duration of the event, etc., they are considered to be manageable on the assumption that information on the incidence of skin erosion in the clinical study and methods for patient management is provided to healthcare professionals appropriately.

7.R.3.2.3 Tumorigenesis

The applicant's explanation about the risk of tumorigenesis:
Results of nonclinical studies suggest that the cells comprising JACEMIN do not have tumorigenicity [see Section 6], and Study ACE02 did not detect any neoplastic lesion at the site of JACEMIN

transplantation. Therefore, tumorigenesis after JACEMIN transplantation would be unlikely to poses a clinical problem.

It is unnecessary to raise caution against tumorigenesis in the package insert, etc. Nevertheless, neoplastic lesion at the graft recipient site will be included in the safety specifications in post-marketing surveillance, and relevant information will be collected.

PMDA's view:
Although there are no findings suggestive of tumorigenicity of JACEMIN in the data of the clinical study or the nonclinical studies, information on tumorigenesis should be carefully collected after the market launch.

7.R.4 Clinical positioning and indication or performance

The proposed "Indication or Performance" was "stable vitiligo (vitiligo vulgaris or piebaldism)." "Precautions Concerning Indication or Performance" had not been proposed.

On the basis of reviews in Sections "7.R.2 Efficacy," "7.R.3 Safety," and the review presented below, PMDA concluded that the "Indication or Performance" section and the "Precautions Concerning Indication or Performance" should be specified as shown below:

Indication or Performance (Underline denotes additions, and strikethrough denotes deletions.)
~~Stable~~ V~~v~~itiligo ~~(vitiligo vulgaris or piebaldism)~~ for which nonsurgical treatment is ineffective or not indicated

Precautions Concerning Indication or Performance (Underline denotes additions.)

- JACEMIN should be used for the treatment of vitiligo vulgaris that is stable for approximately 12 months, spots of complete depigmentation caused by Vogt-Koyanagi-Harada disease or chemical substances, or spots of complete depigmentation due to congenital abnormality such as piebaldism.
- Patients considered appropriate to receive JACEMIN should be selected by physicians with a full understanding of information presented in the "Clinical Studies" section, i.e., the characteristics (conditions of vitiligo, etc.) of patients enrolled in the clinical study and results of JACEMIN transplantation, as well as the mechanism of action, efficacy, and safety of JACEMIN.

7.R.4.1 Clinical positioning and patients treatable with JACEMIN

The applicant's explanation about the clinical positioning of JACEMIN:
Stable vitiligo in patients with vitiligo vulgaris is (a) expansion or regression of existing vitiligo, (b) occurrence of new vitiligo, or (c) vitiligo in patients without Koebner's phenomenon for approximately 12 months. It is refractory to nonsurgical treatments such as topical steroid and phototherapy, and rarely improves by continued treatment (*Microskin Grafting for Vitiligo.* Springer Science+Business Media B.V.;2009:p.7-9). Similarly, vitiligo in patients with piebaldism is a refractory disease unresponsive to nonsurgical treatment such as topical steroid and PUVA therapy (*Comprehensive Handbook of Clinical Dermatology 8. Dyschromatosis*. First edition. Nakayama Shoten, Co., Ltd.; 2002:p.151-4). Surgical treatments conducted in Japan for patients with stable vitiligo vulgaris or piebaldism include, among

others, split-thickness skin grafting, suction blister grafting, and punctate full thickness skin grafting. All of them are autologous skin grafting and fraught with the following problems: (1) Adverse events occur both at the site of skin harvesting and at the site of skin grafting, and (2) only a limited area is available for each single treatment, necessitating multiple treatments.

JACEMIN has demonstrated its efficacy and safety in Study ACE02 and provides a novel treatment option for stable vitiligo, given the following:

- JACEMIN is manufactured by cultivation of skin tissue of small area and allows the treatment of a wide area of vitiligo in a single treatment, thus providing a minimally invasive treatment method compared with other surgical treatment.
- The repigmentation rate exceeded 50% in 6 of 24 subjects, with the repigmentation pattern rated as "uniform" and the extent of color matching as "equal," despite the prohibition of phototherapy, etc. in Study ACE02, suggesting that the treatment effect is expected with JACEMIN monotherapy without the combined use of phototherapy, etc.

The applicant agreed to change the proposed "Indication or Performance" (stable vitiligo [vitiligo vulgaris or piebaldism]) as shown below, based on the discussion with PMDA during the review process:

JACEMIN allows repigmentation at the site of melanocyte-devoid vitiligo without migration of melanocytes from the surrounding normal skin, according to the following mechanism: Following the abrasion of the surface layer of the vitiligous area, JACEMIN is engrafted onto the abraded site, providing melanocytes with epidermal cells and leading to repigmentation. JACEMIN is thus applicable to diseases-related vitiligo that is caused by decreased or missing melanocytes but does not show abnormality in melanosomes or melanin production or migration to epidermal cells (vitiligo vulgaris, Vogt-Koyanagi-Harada disease, depigmented spots caused by chemical substances, piebaldism, and Waardenburg syndrome). Since transplantation of JACEMIN to active vitiligo may result in depigmentation again, only stable vitiligo should be treated with JACEMIN. The "Indication or Performance" and "Precautions Concerning Indication or Performance" should include the followings:

Indication or Performance (Underline denotes additions, and strikethrough denotes deletions.)
Stable vitiligo ~~(vitiligo vulgaris or piebaldism)~~

- JACEMIN is applied to stable vitiligo after abrasion of the epidermis with the aim of skin repigmentation.

Precautions Concerning Indication or Performance (Underline denotes additions.)
JACEMIN should be applied to vitiligo vulgaris that is stable for approximately 12 months, spots of complete depigmentation caused by chemical substances, or piebaldism.

PMDA's view:
Since Study ACE02 demonstrated the efficacy of JACEMIN in the treatment of stable vitiligo, JACEMIN was considered to be positioned as a novel treatment option for stable vitiligo. The treatment with JACEMIN is a surgical treatment accompanied by epidermal abrasion, and stable vitiligo is the intended indication for the treatment with JACEMIN. The "Indication or Performance" should therefore

be clearly defined as “vitiligo for which nonsurgical treatment is ineffective or not indicated.” Since Study ACE02 was conducted in patients with vitiligo with symptoms stabilized for ≥12 months, JACEMIN should be used for vitiligo with symptoms stabilized for approximately 12 months. This caution should be given in the “Precautions Concerning Indication or Performance” section.

The following applicant’s explanation is acceptable: For the types of vitiligo treatable with JACEMIN, the treatment with JACEMIN is expected to show efficacy for diseases producing vitiligo that are caused by melanocyte depletion or decrease not accompanied by abnormalities in melanosomes or melanin production or migration to epidermal cells, since JACEMIN provides epidermal cells including melanocytes by transplantation after abrasion of the epidermal layer of stable vitiligo. If the causative disease of vitiligo is adequately controlled, there is no problem in indicating JACEMIN for the vitiligo. However, the objective of vitiligo treatment by JACEMIN transplantation is cosmetic improvement, and the treatment with JACEMIN should be determined with the understanding of the mechanism of action, efficacy, and safety of JACEMIN. The “Clinical Study” section of the package insert should include the characteristics (condition of vitiligo, etc.) of patients in Study ACE02 and details of results of JACEMIN transplantation, including the results of efficacy endpoints other than the repigmentation rate. Also, the “Precautions Concerning Indication or Performance” section should include the statement that patients must be selected by physicians with a full understanding of the content in the “Clinical Study” section as well as the mechanism of action, efficacy and safety of JACEMIN.

7.R.4.2 JACEMIN transplantation in children

JACEMIN is assumed to be used in children as well. Therefore, PMDA asked the applicant to explain the treatment results in children and cautions uniquely required for children, if any.

The applicant’s explanation:

Study ACE02 included 4 children aged <15 years (hereinafter referred to as “pediatric population”). They were 12 to 13 years old. As for the efficacy in the pediatric population, the repigmentation rate (mean ± SD) at Week 52 after JACEMIN transplantation (the primary endpoint) was 93.8% ± 7.3%. There was no noteworthy tendency in the results with the pediatric population for the secondary efficacy endpoint. As for the safety, there were no events unique to the pediatric population. Adverse events observed at a high incidence in the pediatric population were skin erosion (4 subjects [100.0%]) and pruritus (3 subjects [75.0%]). All were Grade 1 or 2 in severity. All adverse events resolved without any problems during follow up or after additional treatments. No hypertrophic scar was observed.

These results suggest no events requiring particular caution in children at present. However, because only 4 children were enrolled in Study ACE02, JACEMIN should be applied carefully to children after the market launch and patients should be carefully monitored after transplantation.

PMDA’s view:

PMDA accepted the following explanations of the applicant: (1) Results of Study ACE02 suggested the efficacy of JACEMIN in the pediatric population; and (2) as for safety, although some adverse events occurred at a high incidence but they were of low severity grade, posing no particular safety concerns

at present. However, because of the extremely limited number of subjects investigated in the clinical study, information should be collected continuously after the market launch.

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

The "Dosage and Administration or Method of Use" had been proposed as shown below, on the basis of the protocol in Study ACE02.

Dosage and Administration or Method of Use

Operations before the manufacture of epidermal cell sheet

Normal skin tissue (not containing the lesion) of the patient is harvested. The harvested skin tissue is ≥1 cm^2 in size as a guide, and the area of the skin harvested varies depending on the number of the sheets required for transplantation. The harvested skin should be whole-layer skin containing the dermis and spindle-shaped for easy suturing. The normal skin tissue thus harvested is placed in a tissue transport tube, immersed in the transport medium, and transported to the manufacturer.

Operations in epidermal cell sheet transplantation

The epidermis at the target site of the epidermal cell sheet transplantation is abraded by CO_2 laser, a grinder, etc. The epidermal cell sheet is transplanted onto the abraded site. The transplant site is protected by a suitable wound dressing material and immobilized using a plaster cast or Schiene, as necessary.

PMDA concluded that it is acceptable to define the "Dosage and Administration or Method of Use" based on the Study ACE02 which demonstrated the clinical usefulness of JACEMIN. However, as a result of the following review, PMDA concluded that the "Dosage and Administration or Method of Use" should be specified as shown below.

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

Operations before the manufacture of epidermal cell sheet

Normal skin tissue (<u>all-layer skin containing dermis and</u> not containing the lesion) of the patient is harvested <u>according to the transplantation plan</u>. The harvested skin tissue ~~is~~ <u>should be</u> ≥1 cm^2 in size ~~as a guide, and the area of the skin harvested varies depending on the number of the sheets required for transplantation. The harvested skin should be whole-layer skin containing the dermis~~ and spindle-shaped for easy suturing. The normal skin tissue thus harvested is placed in a tissue transport tube, immersed in the transport medium, and transported to the manufacturer.

Operations in epidermal cell sheet transplantation

The epidermis at the target site of the epidermal cell sheet transplantation is abraded ~~by CO_2 laser, a grinder, etc~~. The epidermal cell sheet is transplanted onto the abraded site. ~~The transplant site is protected by a suitable wound dressing material and immobilized using a plaster cast or Schiene, as necessary.~~

7.R.5.1 Harvesting skin tissue and treatment before and after JACEMIN transplantation

The applicant's explanation about the procedures and other necessary information for harvesting skin tissue and treatment before and after JACEMIN transplantation:

Skin tissue is harvested according to the method employed in the preparation of JACE. Thus, the normal skin tissue (not containing the lesion) of the full thickness of at least 1 cm^2 in size including the dermis is harvested according to the number of sheets to be transplanted. Since the area of the harvested skin is determined as a general rule by the number of sheets manufactured according to the transplantation plan, the total of harvested areas is the same, regardless of the number of times of transplantation as far as an equal number of sheets are manufactured. In Study ACE02, the harvested area ranged from 0.5 to 2.5 cm^2, and the number of manufactured sheets was from 2 to 6 and the number of transplanted sheets from 1 to 3.

Prior to JACEMIN transplantation, the area corresponding to epidermis of vitiligo, the treatment target, is abraded by CO_2 laser, etc. Taking account of the adverse events observed associated with epidermal abrasion in Study ACE02, precautionary information will be provided to healthcare professionals by means of materials, advising that the epidermal abrasion should be performed carefully by checking the condition of the site and depth of the abrasion, also by referring to the technique of split-thickness skin grafting in Study ACE02. Also, in order to facilitate safer epidermal abrasion depending on the graft recipient site and the skin conditions, information on epidermal abrading (including the proper device) after marketing will be collected and the information on proper use, if any, will be provided to healthcare professionals in an appropriate manner.

Regarding the treatment after JACEMIN transplantation, the proposed "Dosage and Administration or Method of Use" had stated that "The transplant site is protected by a suitable wound dressing material and immobilized using a plaster cast or Schiene, as necessary." However, this precaution will be included in the "Precautions Concerning Dosage and Administration or Method of Use" section, as is the case with JACE which uses the same protective method as that of JACEMIN.

PMDA's view:

The skin tissue is harvested by the same method as that used for JACE, but the harvesting area varies depending on the number of epidermal cell sheets manufactured. The "Dosage and Administration or Method of Use" section should clearly state that the epidermal tissue should be harvested appropriately according to the transplantation plan.

As for the procedures before and after JACEMIN transplantation, as discussed in Section "7.R.3 Safety," adverse events occurred in Study ACE02 due to scratching to soothe pruritus associated with wound healing after epidermal abrasion and JACEMIN transplantation, and information related to epidermal abrasion in Study ACE02 and patient management after JACEMIN transplantation should be provided to healthcare professionals in an appropriate manner. Devices used for epidermal abrasion and skin protection after JACEMIN transplantation should be selected and used appropriately by the attending physician depending on the site of transplantation and skin conditions of each patient. Therefore, instead of specifying the devices and procedures in the "Dosage and Administration or Method of Use" section,

they should be described in the “Precautions Concerning Dosage and Administration or Method of Use” section for precaution.

7.R.5.2 Number of JACEMIN sheets transplanted in each treatment

PMDA asked the applicant to explain the number of JACEMIN sheets that can be transplanted in a single treatment.

The applicant’s response:

In Study ACE 02, 1 to 3 sheets of JACEMIN were transplanted in each treatment, and efficacy at the transplant site was demonstrated, regardless of the number of sheets transplanted. On the other hand, from the safety point of view, the maximum number of JACEMIN sheets transplanted per treatment was determined to be 50 from the safety evaluation of the process-derived impurities (bovine serum [fetal bovine serum, calf serum, and bovine serum], feeder cells, Impurity A, and antibiotics [amphotericin B, kanamycin sulfate, benzylpenicillin potassium, streptomycin sulfate]) [see Section 6.2.2].

PMDA’s view:

Information on the number of JACEMIN sheets transplanted in Study ACE02 should be provided in an appropriate manner. The applicant’s explanation that the maximum number of JACEMIN sheets in each treatment should be 50 from the safety evaluation of the process-derived impurities is acceptable.

7.R.5.3 Multiple JACEMIN transplantation

PMDA asked the applicant to explain the efficacy and safety in multiple JACEMIN transplantation.

The applicant’s explanation:

Transplantation of JACEMIN to a site different from the initial graft recipient site

When there are multiple sites requiring treatment, there may be cases where JACEMIN is transplanted on multiple days because of the limitation of the area treatable at one time due to the difference in the body posture required for transplantation, etc. The interval of transplantation is determined by taking account of the patient’s burden and convenience. Since the number of sheets per recipient area is the same both at the first and at the second and subsequent recipient sites, a similar extent of efficacy is expected in all of the multiple transplantation.

Re-transplantation of JACEMIN to the initial graft recipient site

If JACEMIN was not successfully engrafted after the initial treatment due to infection, etc., it may be transplanted again onto the identical site. Since it takes ≥1 week to confirm the failure of JACEMIN transplantation and [redacted] days to cultivate epidermal cells in a sheet form after re-transplantation is decided, an interval of ≥2 weeks will be necessary before re-transplantation of JACEMIN to the identical site. Before the re-transplantation, the graft recipient site will be checked for control of infection, etc., to confirm the suitability for transplantation.

JACEMIN may be re-transplanted to the identical site if no repigmentation is observed after the initial transplantation and there is no possibility of changing from the stable state to activated state. Time course of repigmentation varies depending on patients. Usually, results stabilize at 1 year after transplantation,

allowing the assessment of the treatment result. It is thus expected that re-transplantation to the identical site will occur after approximately 1 year after the initial transplantation.

Since there is no difference in the mechanism of supply of melanocytes to each site of JACEMIN transplantation, efficacy similar to that of the initial transplantation is expected, regardless of the interval of transplantation.

Safety of JACEMIN in multiple transplantation
There was no case of multiple JACEMIN transplantation in Study ACE02. However, regardless of whether JACEMIN is transplanted to a site identical to, or different from, the initial graft recipient site, the amount of the residual process-derived impurities in JACEMIN is sufficiently low. In addition, no particular problems have been noted in clinical experience of multiple transplantation of JACE which is made from the same raw materials as those of JACEMIN. There are no safety concerns in multiple transplantation of JACEMIN, precluding the necessity of limiting the total number of sheets transplanted. On the other hand, the possibility cannot be excluded that allergic reactions are induced after the second or subsequent transplantation by components of animal origin, due to the sensitization at the initial transplantation. Caution will be raised in the package insert that patients should be carefully monitored for anaphylactic reaction after transplantation and that appropriate measures should be taken as necessary.

PMDA's view:
The applicant's explanation about multiple JACEMIN transplantation is understandable to a certain extent. However, because of no experience of multiple transplantation at present, information on the efficacy and safety of JACEMIN in multiple transplantation should be collected after the market launch.

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

The applicant's explanation about the post-marketing use-results survey:
The applicant plans to conduct a use-result survey covering all patients treated with JACEMIN in order to confirm the safety and efficacy of JACEMIN in clinical use after the market launch.

The safety specifications in this survey will include "hypertrophic scar at the graft recipient site," "neoplastic lesion at the graft recipient site," "allergic symptoms," and "infection of unknown cause" as risks expected to occur after the market launch of JACEMIN.

The planned sample size is approximately 160 patients per year, taking account of the expected number of patients treated with JACEMIN after the market launch.

The observation period is up to Week 52 after JACEMIN transplantation to allow assessment of each specification in this surveillance, taking account of the results from Study ACE02. For the re-transplantation of JACEMIN to a site identical to, or different from, the initial graft recipient site, the observation period will be from the last transplantation to Week 52.

PMDA's view:

Because of the extremely limited use experience, after the market launch of JACEMIN, a use-results survey covering all patients treated with JACEMIN should be conducted to collect information on the safety and efficacy of JACEMIN promptly and by an unbiased manner. The applicant's above explanation about the survey plan (safety specifications, planned sample size, and observation period) is acceptable. In the use-results survey, information on additional therapy (such as phototherapy) after JACEMIN transplantation should be collected. If there are cases of re-transplantation of JACEMIN, information on such cases, including the background leading to the re-transplantation should be collected and evaluated appropriately. Information that suggests populations or events requiring attention, if any, should be provided to healthcare professionals promptly and appropriately.

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

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

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

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

The new regenerative medical product application data (Attached document 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.

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

On the basis of the data submitted, PMDA has concluded that JACEMIN has a certain level of efficacy in the treatment of vitiligo for which nonsurgical treatment is ineffective or not indicated, and that JACEMIN has acceptable safety in view of its benefits. JACEMIN available in clinical practice is meaningful because it provides a new treatment option for vitiligo for which nonsurgical treatment is ineffective or not indicated.

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

Review Report (2)

January 31, 2023

Product Submitted for Approval

Brand Name	JACEMIN
Non-proprietary Name	Melanocyte-containing Human (Autologous) Epidermis-derived Cell Sheet
Applicant	Japan Tissue Engineering Co., Ltd.
Date of Application	April 27, 2022

List of Abbreviations
See Appendix.

1. Content of the Review

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

1.1 Efficacy

As a result of the review in Section "7.R.2 Efficacy" of the Review Report (1), PMDA has concluded that JACEMIN was shown to have a certain level of efficacy in patients with stable vitiligo.

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 adverse event requiring a particular caution in JACEMIN transplantation is hypertrophic scar. PMDA also concluded that the risk associated with JACEMIN transplantation is acceptable, given the following actions: (1) Provision of appropriate information on adverse events observed in Study ACE02 to healthcare professionals by means of materials and (2) appropriate measures such as monitoring and controlling of adverse events taken by a physician with sufficient knowledge and experience in the treatment of vitiligo and surgical treatment of skin based on said information.

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

1.3 Clinical positioning, indication, or performance

As a result of the review in Section "7.R.4 Clinical positioning and indication or performance" of the Review Report (1), PMDA concluded that the characteristics (conditions of vitiligo, etc.) of patients in Study ACE02 and the results of JACEMIN transplantation including the repigmentation rate and other efficacy endpoints should be detailed in the "Clinical Studies" section of the package insert, and that the "Indication or Performance" and "Precautions Concerning Indication or Performance" sections should be described as shown below, as per the relevant sections of the Review Report (1).

Indication or Performance

Vitiligo for which nonsurgical treatment is ineffective or not indicated

Precautions Concerning Indication or Performance

- JACEMIN should be used for the treatment of vitiligo vulgaris that is stable for approximately 12 months, spots of complete depigmentation caused by Vogt-Koyanagi-Harada disease or chemical substances, or spots of complete depigmentation due to congenital abnormality such as piebaldism.
- Patients considered appropriate to receive JACEMIN should be selected by physicians with a full understanding of information presented in the "Clinical Studies" section, i.e., the characteristics (conditions of vitiligo, etc.) of patients enrolled in the clinical study and results of JACEMIN transplantation, as well as the mechanism of action, efficacy, and safety of JACEMIN.

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

PMDA requested the applicant to modify the "Indication or Performance" and "Precautions Concerning Indication or Performance" sections as described above. As the applicant appropriately responded to the request, PMDA accepted.

1.4 Dosage and administration or method of use

As a result of the review in Section "7.R.5 Dosage and administration or method of use" of the Review Report (1), PMDA has concluded that the "Dosage and Administration or Method of Use" of JACEMIN should be specified as shown below, as described in the relevant section of the Review Report (1).

Dosage and Administration or Method of Use

Operations before the manufacture of epidermal cell sheet

Normal skin tissue (all-layer skin containing dermis and not containing the lesion) of the patient is harvested according to the transplantation plan. The harvested skin tissue should be ≥1 cm^2 in size and spindle-shaped for easy suturing. The normal skin tissue thus harvested is placed in a tissue transport tube, immersed in the transport medium, and transported to the manufacturer.

Operations in epidermal cell sheet transplantation

The epidermis at the target site of the epidermal cell sheet transplantation is abraded. The epidermal cell sheet is transplanted onto the abraded site.

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

PMDA requested the applicant to modify the "Dosage and Administration or Method of Use" section as described above. As the applicant appropriately responded to the request, PMDA accepted.

1.5 Post-marketing surveillance plan (draft)

PMDA concluded that post-marketing surveillance should be conducted covering all patients receiving JACEMIN, using the following safety specifications: "Hypertrophic scar at the graft recipient site," "neoplastic lesion at the graft recipient site," "allergic symptoms," and "infection of unknown cause," as described in Section "8. Risk Analysis and Outline of the Review Conducted by PMDA" of the Review Report (1).

At the expert discussion, the expert advisors proposed that skin erosion be included in the safety specifications. Taking account of the facts that skin erosion was observed in 11 of 23 subjects (45.8%) in Study ACE02 and that skin ulcer is a potential risk of JACEMIN, PMDA concluded that skin erosion and skin ulcer should be added to safety specifications. This conclusion of PMDA was supported by the expert advisors.

PMDA requested the applicant to modify the post-marketing surveillance plan based on the results of the Expert Discussion. In response, the applicant submitted an outline of the post-marketing surveillance plan (draft) shown in Table 26, and PMDA accepted the draft plan. The applicant explained that the number of patients likely to use JACEMIN was re-evaluated by taking account of patients with the causative disease of vitiligo, the disease for which JACEMIN is indicated, and that the planned sample size was corrected to approximately 170 patients per year.

Table 26. Outline of post-marketing surveillance plan (draft)

Objective	To investigate the safety of JACEMIN in clinical use
Survey method	All-case surveillance
Observation period	Up to Week 52 after JACEMIN transplantation
Population	Patients with vitiligo for which nonsurgical treatment is ineffective or not indicated
Planned sample size	Approx. 170 patients/year
Main survey items	Safety specifications Hypertrophic scar at the graft recipient site, skin erosion and skin ulcer at the graft recipient site, neoplastic lesion at the graft recipient site, allergic symptoms, and infection of unknown cause

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 Notification 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 JACEMIN should be designated as a specified regenerative medical product because (1) murine cells (3T3-J2) are used as feeder cells in the manufacture process and (2) pathogens are not inactivated or removed in the manufacturing process of JACEMIN, although JACEMIN is a product manufactured by using the autologous skin tissue as the starting material.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the indication or performance and the dosage and administration or method of use as shown below, with the following approval conditions. The re-examination period is 8 years. The product is designated as a specified regenerative medical product.

Indication or Performance

Vitiligo for which nonsurgical treatment is ineffective or not indicated

Dosage and Administration or Method of Use

Operations before the manufacture of epidermal cell sheet

Normal skin tissue (all-layer skin containing dermis and not containing the lesion) of the patient is harvested according to the transplantation plan. The harvested skin tissue should be ≥1 cm^2 in size and spindle-shaped for easy suturing. The normal skin tissue thus harvested is placed in a tissue transport tube, immersed in the transport medium, and transported to the manufacturer.

Operations in epidermal cell sheet transplantation

The epidermis at the target site of the epidermal cell sheet transplantation is abraded. The epidermal cell sheet is transplanted onto the abraded site.

Approval Conditions

1. Because the number of patients participating in the clinical trial is very limited, the applicant is required to conduct a use-results survey covering all patients treated with the product, in principle, until the end of the re-examination period, in order to identify the characteristics of patients using the product and promptly collect safety and efficacy data of the product, thereby taking necessary measures to ensure the proper use of the product.
2. Taking account of the risk associated with heterologous transplantation of murine embryonic 3T3-J2 cells used as the feeder cells during the manufacturing process of the product, the applicant is required to take necessary measures such as storage of the final product samples and retention of use records for 30 years to ensure the proper handling of the product.

Appendix

List of Abbreviations

3T3-J2 cells	Mouse embryonic cells
Application	Application for marketing approval
[redacted]	[redacted]
CI	confidence interval
[redacted]	[redacted]
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q5A (R1) Guideline	"Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (PMSB/ELD Notification No. 329 dated February 22, 2000)
ICH Q5D Guideline	"Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products" (PMSB/ELD Notification No. 873 dated July 14, 2000).
[redacted]	[redacted]
MCB	master cell bank
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MRC-5 cells	Human fetal lung fibroblasts
[redacted]	[redacted]
MWCB	master working cell bank
NIH-3T3 cells	Mouse embryonic cells
[redacted]	[redacted]
PMDA	Pharmaceuticals and Medical Devices Agency
PUVA	psoralen and ultraviolet A
QOL	quality of life
Study ACE02	Study J-TEC-ACE02
[redacted]	[redacted]
UVB	ultraviolet B
[redacted]	[redacted]
Vero cells	African green monkey kidney epithelial cells
WCB	Working cell bank