Report on the Deliberation Results

September 16, 2016

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

Classification	Human cellular/tissue-based products, 1 Human somatic cell-processed products
Non-proprietary Name	Human (autologous) epidermal cell sheet
Brand Name	JACE
Applicant	Japan Tissue Engineering Co., Ltd. (J-TEC)
Date of Application	January 29, 2016 (partial change approval application)

Results of Deliberation

In its meeting held on September 16, 2016, the Committee on Regenerative Medicine Products and Biotechnology made the following decision and concluded that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

A regenerative medical product, JACE, may be approved. A conditional and time-limited approval is not applicable to the product. The re-examination period is 10 years.

The following conditions of approval should be imposed.

Conditions of Approval

1. Because the clinical studies were conducted in extremely limited number of subjects, the applicant is required to conduct a use-results survey covering all patients treated with the product. As a rule, the survey should be continued until the end of the re-examination period. New efficacy and safety data on the product should be communicated appropriately to surgeons/physicians and medical institutions providing treatment with the product, and patient information materials should be updated with the data accordingly.
2. Due to the risks associated with xenotransplantation of 3T3-J2 cells derived from mouse embryo, which are used as feeder cells in the manufacture of the product, the applicant is required to take necessary measures to ensure appropriate handling, such as 30-year retention of a sample of the finished product and a record of use.

Review Report

September 1, 2016
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following regenerative medical product submitted for partial change approval conducted by the Pharmaceuticals and Medical Devices Agency.

Brand Name JACE

Classification Human cellular/tissue-based products, 1 Human somatic cell-processed products

Non-proprietary Name Human (autologous) epidermal cell sheet

Applicant Japan Tissue Engineering Co., Ltd. (J-TEC)

Date of Application January 29, 2016

Shape, Structure, Active Ingredient, Quantities, or Definition

An epidermal cell sheet supplied in the package for cultured epidermis is "autologous cultured epidermis" produced from keratinocytes isolated from a patient's own skin tissue. The isolated keratinocytes are cultured into cell sheets for autografting. Cultured (autologous) epidermal cell sheets are grafted onto the wound surface with preserved dermis for the closure of the wound via engraftment/epithelialization. Each container for cultured epidermis contains 1 piece of cultured epidermal cell sheet. A tissue transport tube is used to store and transport the harvested tissue.

Application Classification (3) Regenerative medical product with a new indication

Items Warranting Special Mention

Orphan regenerative medical product (Designation No. 1 of 2014 [*26 sai*]; Notification No. 1125-17 dated November 25, 2014, issued by the Counselor for Medical Device and Regenerative Medicine Product Evaluation, Minister's Secretariat, Ministry of Health, Labour and Welfare)

Reviewing Office Office of Cellular and Tissue-based Products

Results of Review

The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the data submitted demonstrate the efficacy of the product in the closure of wounds after the excision of giant congenital melanocytic nevi and acceptable safety in view of the benefits indicated by the data submitted, as shown in Attachment.

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

Indication or Performance

1. Severe burns

JACE is indicated for use in patients with serious, extensive burns when sufficient donor sites for autologous skin grafts are not available and the total area of deep dermal and full-thickness burns is 30% or more of the total body surface area. A cultured epidermal cell sheet is applied onto the reconstructed dermis in a full-thickness burn wound to facilitate the closure of the wound. Dermis should be reconstructed with allografts, as a general rule. JACE should be used for deep dermal burn wounds only when full-thickness and deep dermal burns coexist and it is difficult to treat them separately.

2. Giant congenital melanocytic nevi

The cultured epidermal cell sheet is applied onto a wound after excision of giant congenital melanocytic nevi to facilitate the closure of the wound.

(Underline denotes additions.)

Dosage and Administration or Method of Use

Grafting plan

1. Grafting plan

A treating surgeon/physician develops a grafting plan and provides the manufacturer of JACE with the details of the plan, which consist of the number of cultured epidermal cell sheets required, the dates of tissue harvest and grafting, the number of grafting procedures, and other necessary information such as on the medical institution and the patient (hereinafter collectively referred to as the "grafting planning information"). The manufacturer prepares an order form indicating a tissue code unique to each grafting plan and the grafting planning information, then send it to the treating surgeon/physician.

The treating surgeon/physician confirms the grafting planning information entered in the order form sent by the manufacturer, before placing an order for production of JACE.

The manufacturer supplies the surgeon/physician with a tissue transport kit (comprising tissue transport tubes) and a dedicated heat-insulating container in time for the date of tissue harvest. The tissue code is indicated on the carton of the tissue transport kit, tissue transport tubes, and heat-insulating container for tissue transportation provided by the manufacturer.

Tissue code

Tissue codes are issued for each grafting plan.

For a patient undergoing tissue harvest more than once, each piece of tissue harvested is identified by a unique tissue code. A grafting plan is developed on a tissue-code basis.

For a patient undergoing a single tissue harvest followed by serial grafting procedures, cultured epidermal cell sheets for multiple grafting procedures are produced using cells derived from the same skin tissue. The tissue code remains unchanged for production of such sheets. Therefore, these sheets are identified with the same tissue code and different batch numbers.

Steps from tissue harvest at the medical institution through the receipt of harvested tissue

2. Tissue harvest

Skin tissue is harvested based on the size of the graft recipient site and according to the grafting plan. The harvested skin should be at least 1 cm^2 in size and elliptical in shape or in such a shape that allows for easier suture. Skin tissue is taken from lesion-free normal skin at any anatomical site. The full-thickness of dermis should be harvested from the donor site.

3. Storage of harvested tissue

The sealing band on the heat-insulating container is cut with scissors to remove the lid and take out the tissue transport kit. The tissue code indicated on the heat-insulating container, carton of the tissue transport kit, and tissue transport tubes is checked against the order form.

The tissue transport kit is unsealed in a clean environment (e.g., operating room, procedure room) to take out the transport tube. The tube is checked for leakage and turbidity of the medium filled in it. If the medium is turbid, the spare tube is used.

The tissue transport tube should not be tilted or shaken unnecessarily.

The tissue transport tube is uncapped. The skin tissue, harvested in a clean environment, is placed in the tube using sterile forceps, etc. to be immersed in the medium. The tube is then capped tightly to prevent a leak of the medium. The date of tissue harvest and the name of the person who performed harvest are indicated on the tube.

4. Transportation of harvested tissue

The tissue transport tube is placed in the carton. The carton is sealed for tamper resistance and placed in the heat-insulating container (temperature during transportation, 4°C to 25°C). The container is sealed with 4 sealing bands for delivery to the manufacturer. The manufacturer should receive the skin tissue within 62 hours after the heat-insulating container has been shipped to the medical institution [see “1. Grafting plan”].

Note: Presumably, each medical institution will follow its own procedure for handling harvested skin tissue and JACE (e.g., special procedures, responsible department). Therefore, the distributor will undertake the transportation of harvested skin tissue and JACE under the supervision of the manufacturer until a reliable system is established and maintained for the delivery and acceptance of harvested skin tissue and JACE. Once such a system is fully in place, part of the transportation process will be outsourced to a logistics company

while the distributor will still be responsible for the rest of the process.

Steps from release at the manufacturer through acceptance at the medical institution

5. Acceptance inspection and handling of the product at the medical institution

(1) A package of cultured epidermis is shipped in a heat-insulating container sealed with bands. The medical institution must ensure that the container is kept sealed before use.

The heat-insulating container is unpacked by cutting the sealing bands with scissors to take out the package of cultured epidermis.

(2) The tissue code (5-digit alphanumeric code) incorporated in the batch number on the package is checked against the order form retained at the medical institution (issued in the step as described in "1. Grafting plan"). The number of the cultured epidermal cell sheets is checked.

(3) The package of cultured epidermis is stored at 10°C to 25°C until immediately before use.

Grafting

6. Procedures before grafting of the cultured epidermal cell sheet

(1) Severe burns

Dermal reconstruction is performed on the site to be treated with the cultured epidermal cell sheet.

(2) Giant congenital melanocytic nevi

The lesion (nevus) is excised. The surgical technique for excision is determined according to the patient's age and nevus size. Dermal reconstruction is performed as necessary.

7. Grafting of the cultured epidermal cell sheet

(1) Severe burns

The cultured epidermal cell sheet is applied onto the reconstructed dermis. However, the grafting should be preceded by appropriate wound bed preparation such as the removal of necrotic tissue or other factors that render the recipient wound bed unsuitable for grafting, if any. The cultured epidermal cell sheet may be used on a deep dermal burn wound only when full-thickness and deep dermal burns coexist and it is difficult to treat them separately.

(2) Giant congenital melanocytic nevi

The cultured epidermal cell sheet is applied onto the preserved dermis or reconstructed dermis of a wound after nevus excision.

8. The number of sheets to be grafted in a single procedure or serial procedures

Up to 50 pieces of cultured epidermal cell sheets are allowed to be grafted in a single procedure, and a total of up to 200 cell sheets in serial procedures. The number of cultured epidermal cell sheets used should not exceed these upper limits.

(Underline denotes additions/changes.)

Conditions of Approval

1. Because the clinical studies were conducted in extremely limited number of subjects, the applicant is required to conduct a use-results survey covering all patients treated with the product. As a rule, the survey should be continued until the end of the re-examination period. New efficacy and safety data on the product should be communicated appropriately to surgeons/physicians and medical institutions providing treatment with the product, and patient information materials should be updated with the data accordingly.
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Attachment

Review Report (1)

July 1, 2016

Product Submitted for Approval

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Proposed Indication or Performance

1. Severe burns

JACE is indicated for use in patients with serious, extensive burns when sufficient donor sites for autologous skin grafts are not available and the total area of deep dermal and full-thickness burns is 30% or more of the total body surface area. A cultured epidermal cell sheet is applied onto the reconstructed dermis in a full-thickness burn wound to facilitate the closure of the wound. Dermis should be reconstructed with allografts, as a general rule. JACE should be used for deep dermal burn wounds only when full-thickness and deep dermal burns coexist and it is difficult to treat them separately.

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The cultured epidermal cell sheet is applied onto a wound after excision of giant congenital melanocytic nevi to facilitate the closure of the wound.

(Underline denotes additions.)

Proposed Dosage and Administration or Method of Use

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1. Grafting plan

A treating surgeon/physician develops a grafting plan and provides the manufacturer of JACE with the details of the plan, which consist of the number of cultured epidermal cell sheets required, the dates of tissue harvest

and grafting, the number of grafting procedures, and other necessary information such as on the medical institution and the patient (hereinafter collectively referred to as “the grafting planning information”). The manufacturer prepares an order form indicating a tissue code unique to each grafting plan and the grafting planning information, then send it to the treating surgeon/physician.

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The sealing band on the heat-insulating container is cut with scissors to remove the lid and take out the tissue transport kit. The tissue code indicated on the heat-insulating container, carton of the tissue transport kit, and tissue transport tubes is checked against the order form.

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Note: Presumably, each medical institution will follow its own procedure for handling harvested skin tissue and JACE (special procedures, responsible department, etc.). Therefore, the distributor will undertake the transportation of harvested skin tissue and JACE under the supervision of the manufacturer until a reliable system is established and maintained for the delivery and acceptance of harvested skin tissue and JACE. Once such system is fully in place, part of the transportation process will be outsourced to a logistics company while the distributor will still be responsible for the rest of the process.

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The heat-insulating container is unpacked by cutting the sealing bands with scissors to take out the package of cultured epidermis.

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(3) The package of cultured epidermis is stored at 10°C to 25°C until immediately before use.

Grafting

6. Procedures before grafting of the cultured epidermal cell sheet

(1) Severe burns

Dermal reconstruction is performed on the site to be treated with the cultured epidermal cell sheet.

(2) Giant congenital melanocytic nevi

The lesion (nevus) is excised. The surgical technique for excision is determined according to the patient's age and nevus size. Dermal reconstruction is performed as necessary.

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The cultured epidermal cell sheet is applied onto the preserved dermis or reconstructed dermis of a wound after nevus excision.

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Up to 50 pieces of cultured epidermal cell sheets are allowed to be grafted in a single procedure, and a total of up to 200 pieces of sheets in serial procedures. The number of cultured epidermal cell sheets used should not exceed these upper limits.

(Underline denotes additions/changes.)

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.

Table of Contents

List of Abbreviations

Final epithelialization rate	Epithelialization rate of at the time when wound closure (≥95%) was achieved for the first time after the initial grafting of the cultured epidermal cell sheets
GCMN	Giant congenital melanocytic nevus
PMDA	Pharmaceuticals and Medical Devices Agency
Product	JACE
Retrospective study	Retrospective study based on medical records
Tissue expansion technique	Skin suture following skin expansion with a tissue expander (an expander)

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

1.1 Overview of product submitted for approval

JACE is a combination product. Its primary constituent is a human (autologous) epidermal cell sheet that is produced using the Green's technique and packaged in a primary container. For production of the cultured autologous epidermal cell sheet, keratinocytes are isolated from a postage-stamp sized piece of a patient's own healthy skin tissue and are co-cultured with mouse embryo-derived 3T3-J2 cells as a feeder. The cultured keratinocytes are grown into a sheet. The cell sheet is immersed in storage medium to be released from the manufacturer. The secondary constituent of the product is a tube (filled with tissue transport medium) used to transport skin tissue harvested from the patient to the manufacturer of JACE.

JACE is a regenerative medical product to be used for the closure, early epithelialization, etc. of a wound after excision of a giant congenital melanocytic nevus (GCMN) as with medical devices such as wound dressings. The mechanism of action of the cultured epidermal cell sheet is as follows: (1) Keratinocytes of the sheet come in contact with the wound surface due to graft immobilization on the wound or a simple adhesive force of the exudate of the wound. (2) The keratinocytes in contact with the wound surface produce cell adhesion molecules such as cadherin and adhere to the dermal layer. (3) The keratinocytes begin to proliferate while desmosomes are formed between the cells by desmogleins belonging to the cadherin family. Hemidesmosomes are formed between the keratinocytes and the dermal tissue through the interaction of integrin with laminin-5, resulting in the adhesion of the keratinocytes to the dermal layer. (4) The keratinocytes proliferate repeatedly adhering to the dermal layer until the entire wound is covered.

In Japan, JACE was approved for marketing for the indication of severe burns in October 2007. The product was designated as an orphan regenerative medical product with the intended indication or performance of "early epithelialization of a wound after excision of a giant congenital melanocytic nevus" as of November 25, 2014 (Designation No.1 of 2014 [*26 sai*]).

1.2 Development history, etc.

GCMN is a brown to black pigmented lesion that is present at birth on the trunk, limbs, scalp, or other sites. GCMN is defined as a melanocytic lesion having diameters of ≥20 cm in adults and of ≥6 cm on the trunk or ≥9 cm on the scalp in infants (*Dermatol Clin*. 2002; 20: 607-716, *Rinsho Derma*. 2002; 44: 513-17). GCMN is caused by the accumulation of melanocytes in the dermal-epidermal junction or the dermis. GCMN, which does not fade with age, has the potential to develop into malignant melanoma in future (*Plast Reconstr Surg*. 2009; 124: 1e-13e). In Japan, malignant melanoma occurs in approximately 3% of patients with GCMN, half of whom are diagnosed with malignant melanoma by 3 years of age. Nevi should preferably be excised early in life. An estimated 11,000 to 12,000 individuals have GCMN in Japan (based on MHLW "2011 Patient Survey" [http://www.e-stat.go.jp/SG1/estat/GL08020103.do?
toGL08020103&listID=000001103073&requestSender=dsearch], etc.).

Known treatment options for GCMN include excision and suture, serial excision, skin expansion (skin suture

following skin expansion with a tissue expander [an expander]), skin grafting, laser treatment, and removal of skin tissue containing a nevus with a dermatome or by curettage. These techniques are often used in combination. Generally, the surface of a wound after excision is covered with dressings, etc. until epithelialized. Delayed epithelialization may not only lead to hypertrophic scarring but also result in a risk of infection before epithelialization or poor exudate management. Thus, rapid epithelialization after surgical procedure is essential for more effective healing of a wound with dermis preserved after nevus excision. Recently, published literature reported a case of GCMN treated with cultured epidermal autografts generated using the Green's technique, which were developed by Howard Green et al. of Harvard Medical School (the US) in 1975 (*Dermatol Surg.* 2005; 31:1660-7). The cultured epidermal autograft generated using the Green's technique was approved for the treatment of burns, but not for the closure of nevus excision wounds in any country or region. The applicant started the clinical development of JACE, human autologous epidermal cell sheets, for the closure of nevus excision wounds in patients with GCMN, and recently filed a partial change application for the regenerative medical product.

2. Manufacturing Process and Specifications

Because the present application is intended to expand the indication, data on manufacturing process and specifications were not submitted.

3. Stability

Because the present application is intended to expand the indication, stability data were not submitted.

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

Although the present application is intended to expand the indication, no study data were submitted to support the efficacy or performance of JACE in the treatment of wounds after the excision of GCMN.

The applicant's justification for not conducting an animal model-based study to support the efficacy or performance of JACE used to treat wounds after excision of GCMN:

Generally, animal models of skin wound healing show greater wound contraction than that observed in the healing process in humans. This precludes accurate determination of the rate of epithelialization, and therefore there is no standardized method for the assessment of epithelialization in animal models. Epidermal cell sheets are assumed to be engrafted and epithelialized on a wound after excision of a nevus ("nevus excision wound") in patients with GCMN by the mechanism similar to that on a wound with preserved dermis such as deep dermal burns or full-thickness wound such as full-thickness burn. Thus, the conduct of a new study using an animal model was unnecessary.

In Japan, an investigator-initiated clinical study (Study 3SI-GCMN001) was conducted using JACE to treat wounds with preserved dermis following excision of nevi, and engraftment and epithelialization of the JACE cultured epidermal cell sheets were demonstrated in the study. Nevus excision wounds with preserved dermis present a condition similar to that of deep dermal burn wounds. Thus, the cultured epidermal cell

sheets can be grafted onto nevus excision wounds with preserved dermis. Successful engraftment of donor cells will promote the epithelialization of the wound surface, thereby resulting in rapid wound closure.

Full-thickness excision wounds have no remaining dermis and therefore require dermal reconstruction before grafting of the cultured epidermal cell sheets, as with the treatment for full-thickness burns. In some clinical cases of patients having nevus excision wounds with no dermis, cultured epidermal autografts produced by the Green's technique were transplanted onto the wounds with reconstructed dermis. These patients demonstrated successful closure and healing of the wounds (*Journal of Clinical and Experimental Medicine*. 2002; 200: 243-46, *Japanese Journal of Plastic Surgery.* 1998; 41: 29-37).

4.R Outline of the review conducted by PMDA

PMDA's view on the efficacy or performance of JACE in treating nevus excision wounds in patients with GCMN:

Removal of a nevus with a dermatome or by similar techniques results in the loss of epidermis at the wound site as in the case of a deep dermal or full-thickness burn wound. The proliferation and elongation of epidermal cells around hair follicles contribute to the epithelialization of the damaged skin, but this will not occur in wounds involving the loss of epidermis. The applicant claims that grafting of the cultured epidermal cell sheets onto such an epidermal defect promotes the epithelialization and closure of the wound. The applicant's claim is largely understandable. Because the cultured epidermal cell sheet grafted onto a nevus excision wound in patients with GCMN is considered to exert its action similarly to that on a deep dermal or full-thickness burn wound, the applicant's explanation on the absence of an animal model study is acceptable.

However, the number of patients evaluated in Study 3SI-GCMN001 was very limited (8 patients), and there is no experience with the use of JACE in patients with GCMN who underwent dermal reconstruction. Thus, post-marketing data on the condition of nevus excision wounds before grafting, epithelialization after grafting, etc. should be collected and appropriately communicated to healthcare professionals [see "7. Clinical Data" and "8. Risk Analysis"].

5. Biodistribution of the Product

Because the present application is intended to expand the indication, biodistribution data have not been submitted.

6. Nonclinical Safety Data

Because the present application is intended to expand the indication, nonclinical safety data have not been submitted.

7. Clinical Data and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data from 2 studies: an investigator-initiated Japanese clinical study (Study 3SI-GCMN001) and a follow-up study enrolling patients who were treated with

JACE in Study 3SI-GCMN001 (Study J-TEC-GCMN002).

7.1 Investigator-initiated Japanese clinical study (Attachment 1, Study 3SI-GCMN001 [[redacted] to [redacted]])

A multicenter, open-label, uncontrolled study was conducted at 4 sites in Japan to assess the efficacy and safety of the cultured epidermal cell sheets grafted onto wounds after nevus excision in patients with GCMN who were untreatable or very difficult to treat with conventional techniques.

The inclusion criteria were (1) patients with GCMN, (2) who had a nevus covering approximately ≥5% of the total body surface area and (3) who were ≥3 months of age at the time of grafting and assessed by the adjudication committee as requiring ≥4 procedures with conventional techniques. The target number of subjects was 10.

Details of the study is presented below.

Skin harvest and the production of JACE

To start the production of JACE, a piece of full-thickness skin including dermis (approximately 2 cm^2) is excised from the patient's healthy skin free from nevi or other abnormalities.

Dosage and administration or method of use in this study

A nevus is removed using an appropriate technique (e.g., dermatome excision, curettage) so that a dermal layer can be preserved. The cultured epidermal cell sheets are applied onto the nevus excision wound. At 2 and 3 weeks after the initial grafting, the need of additional grafting are determined. An additional grafting procedure, if necessary, is performed at 3 weeks after the initial grafting.

While the target number of study subjects was 10, the study enrolled 11 subjects. Of these, 8 subjects[1] underwent grafting of the cultured epidermal cell sheets. Table 7-1 shows patient characteristics, data on nevus excision, and the number of cell sheets grafted in each subject.

[1] One subject gave consent but did not undergo skin harvesting. A total of 2 subjects underwent skin harvesting but did not undergo grafting. The subject who did not undergo skin harvesting was 2 years of age and was withdrawn from the treatment, with consideration for a heavy burden on their family in terms of hospital stay and outpatient visits. One of the 2 subjects who did not undergo grafting after skin harvesting had a nevus around the shoulder joint, which could pose a risk of postoperative contracture. The other subject was concerned about the risk of pruritus in the wound healing process after nevus excision.

Table 7-1. Patient characteristics, nevus excision, and number of epidermal cell sheets grafted

Subject ID	Age (months)	Sex	Nevus size (cm^2)	Nevus as a percentage of total body surface area (%) (DuBois formula/Fujimoto formula)	Size of excised nevus (cm^2)	Excised nevus as a percentage of total body surface area (%) (DuBois formula/Fujimoto formula)	Anatomic site excised	Technique used	No. of sheets (initial/ additional)
H-2	32	Male	1320	24.7/23.7	260	4.9/4.7	· Flank · Lower abdomen	· Dermatome excision · Curettage	4/1
H-3	40	Female	345	5.8/5.8	280	4.7/4.7	Lower abdomen	Dermatome excision	4/1
K-1	59	Female	1540	20.6/21.4	91	1.2/1.3	Thoracoabdominal region	Dermatome excision	3/-
K-3	28	Male	524	9.9/9.4	105	2.0/1.9	Back	Dermatome excision	3/-
K-4	26	Male	1720	34.2/32.3	94.5	1.9/1.8	Back	Dermatome excision	2/-
M-1	25	Female	374	8.4/7.6	238	5.3/4.9	Back	Dermatome excision	10/4
M-2	55	Male	576	9.7/9.5	153	2.6/2.5	Back	Dermatome excision	7/-
T-1	7	Female	558	16.3/14.9	78.8	2.3/2.1	Thoracoabdominal region	· Dermatome excision · Scalpel excision · Scissors excision	3/-

The primary efficacy analysis population was the Full Analysis Set (FAS). The safety analysis population consisted of subjects grafted with the cultured epidermal cell sheets. All of the 8 subjects were included in these analysis populations.

The observation period of the efficacy and safety endpoints was from the initial grafting until week 12 post-treatment or discontinuation as a rule. However, for subjects who achieved the epithelialization rate (epithelialized area ÷ grafted area × 100 [%]) of ≥95% at discharge, the observation ended at that point. Subjects who had the epithelialization rate of <95% at discharge were to return for follow-up visit every 4 weeks after discharge until ≥95% epithelialization was achieved. The definition of complete epithelialization was as follows: ≥95% of the grafted area has dried up (dry wound surface with no exudate), requiring no further special treatment under the supervision of a surgeon/physician.

The primary efficacy endpoint was ≥95% epithelialization of grafted area at 12 weeks after the initial grafting of the cultured epidermal cell sheets or the day of discontinuation. The outcome was defined as “effective” if the endpoint was achieved. Because ≥95% epithelialization was achieved in all 8 subjects who had undergone grafting, the efficacy rate was 100%.

Secondary efficacy endpoints were the epithelialization rates at 8 and 12 weeks after the initial grafting, the

epithelialization rate at the time when wound closure (≥95%) was achieved for the first time after the initial grafting of the cultured epidermal cell sheets (the final epithelialization rate), time to complete epithelialization, and the number of days of hospital stay after the initial grafting. The results are shown in Table 7-2.

Table 7-2. Epithelialization rates at 8 and 12 weeks after initial grafting, final epithelialization rates, time to complete epithelialization, and number of days of hospital stay after initial grafting

Subject ID	Epithelialization rate at 8 weeks (%)	Epithelialization rate at 12 weeks (%)	Final epithelialization rate (%)	Time to complete epithelialization (days)	Number of days of hospital stay post-initial grafting
H-2	—	—	98.1	25	25
H-3	—	—	98.2	70	24
K-1	—	—	100.0	14	16
K-3	—	—	100.0	15	15
K-4	—	—	100.0	14	14
M-1	90.0	99.0	99.0	81	53
M-2	—	—	99.0	14	27
T-1	—	—	96.1	14	33

The safety of JACE was assessed based on adverse events, clinical laboratory findings, clinical signs, etc. after grafting of the cultured epidermal cell sheets. The safety assessment criteria presented in Table 7-3 were used for further safety assessment.

Table 7-3. Safety assessment criteria

Very safe	Safe	Not very safe	Unsafe
No adverse events related to the grafting procedure were reported.	Mild adverse event(s) related the grafting procedure was reported. The event(s) required no treatment.	Adverse event(s) related to the grafting procedure was reported. The event(s) was treated and required no prolonged care.	Adverse event(s) related to the grafting procedure was reported. The event(s) required prolonged care.

Adverse events occurred in all of the 8 subjects (Table 7-4).

Table 7-4. Adverse events observed in the study

Subject ID	Adverse event	Number of days from the initial grafting to onset of event	Number of days to outcome	Severity	Seriousness	Outcome	Causal relationship to JACE
H-2	Pain	1	2	Mild	Non-serious	Resolved	Not related
	Ulcer	13	52	Mild	Non-serious	Resolved	Cannot be ruled out
	Worsening eczema	2	63	Mild	Non-serious	Resolved	Not related
H-3	Cellulitis	12	4	Moderate	Non-serious	Resolved	Not related
	Pain	1	2	Mild	Non-serious	Resolved	Not related
	Ulcer	12	60	Mild	Non-serious	Resolving	Cannot be ruled out
	Skin exfoliation	18	54	Mild	Non-serious	Resolved	Cannot be ruled out
K-1	Pain	1	3	Mild	Non-serious	Resolved	Not related
	Itching	1	11	Mild	Non-serious	Resolved	Cannot be ruled out
	Cold	6	10	Mild	Non-serious	Resolved	Not related
K-3	Itching	3	49	Mild	Non-serious	Resolved	Cannot be ruled out
	Skin exfoliation	16	36	Mild	Non-serious	Resolved	Not related
K-4	Stools watery	3	1	Mild	Non-serious	Resolved	Not related
	Nasal discharge	12	2	Mild	Non-serious	Resolved	Not related
	Itching	8	40	Mild	Non-serious	Resolving	Not related
	Pyrexia	1	1	Mild	Non-serious	Resolved	Not related
	Heart rate increased	1	1	Mild	Non-serious	Resolved	Not related
M-1	Pyrexia	1	31	Mild	Non-serious	Resolved	Not related
	Face oedema	2	3	Mild	Non-serious	Resolved	Not related
	Vomiting	1, 9, 23	4, 1, 1	Mild	Non-serious	Resolved	Not related
	Herpes zoster	5	27	Moderate	Non-serious	Resolved	Not related
	Pruritus	8	75	Moderate	Non-serious	Resolving	Not related
	Anaemia	2	49	Mild	Non-serious	Resolved	Not related
	Platelets increased	8	15	Mild	Non-serious	Resolved	Not related
	Protein total decreased	2, 22	7, 29	Mild	Non-serious	Resolved	Not related
M-2	Skin red	3	13	Mild	Non-serious	Resolved	Not related
	Pruritus	2	43	Moderate	Non-serious	Resolving	Not related
	Recipient site infection	21	24	Moderate	Serious	Resolved	Not related
	Red rash	21	7	Moderate	Non-serious	Resolved	Not related
T-1	Postoperative haemorrhage	1	15	Mild	Non-serious	Resolved	Not related
	Vomiting	1, 18	2, 5	Mild	Non-serious	Resolved, Resolving	Not related
	Miliaria on the neck	5	11	Mild	Non-serious	Resolved	Not related
	Diarrhoea	19	4	Mild	Non-serious	Resolved	Not related
	Recipient site erosion	22	121	Mild	Non-serious	Resolved	Cannot be ruled out
	Extension of non-epithelialized area	22	44	Mild	Non-serious	Resolved	Cannot be ruled out
	Pain	1	2	Mild	Non-serious	Resolved	Not related

Recipient site infection occurring in 1 subject was serious, but its causal relationship to JACE was ruled out. There were no deaths or other serious adverse events.

A causal relationship to JACE could not be ruled out for ulcer (2 subjects), itching (2 subjects), skin exfoliation (1 subject), recipient site erosion (1 subject), and extension of non-epithelialized area (1 subject), all of which were mild in severity.

Based on adverse events occurring through 12 weeks after the initial grafting, the safety of JACE was assessed on a 4-point scale using the safety assessment criteria presented in Table 7-3. The product was rated as "very safe" in 3 subjects (K-4, M-1, and M-2), "safe" in 2 subjects (H-2 and T-1), "not very safe" in 3 subjects (H-3, K-1, and K-3), and "unsafe" in none of the subjects.

Ulcer, itching, skin exfoliation, and recipient site erosion were rated as "not very safe" and a causal relationship to the product could not be ruled out for these events. However, all these events were mild in severity.[2]

7.2 Follow-up study in patients who were treated with JACE in the investigator-initiated Japanese clinical study (Study 3SI-GCMN001) (Attachment 2, Study J-TEC-GCMN002 [to])

A multicenter, open-label, uncontrolled study was conducted at 4 sites in Japan. The study assessed the long-term safety of JACE in patients who were treated with JACE in Study 3SI-GCMN001.

All of 8 subjects who had undergone the grafting in Study 3SI-GCMN001 were enrolled in this study and included in the safety analysis population.

The observation period of this study was from complete epithelialization until 1 year after the initial grafting. Endpoints were (1) the condition of the grafted area at 6 months and 1 year post-initial grafting (erosion, ulceration, scar contracture, and infection at the graft recipient site), (2) adverse events, (3) clinical signs, (4) clinical laboratory tests, and (5) the occurrence of neoplastic lesions at the graft recipient site, allergic symptoms, and infection for which a causal relationship to the product could not be ruled out.

The primary endpoints were (1) the condition of the graft recipient site after complete epithelialization, (2) the occurrence of adverse events and malfunctions, and (3) safety assessment according to the criteria presented in Table 7-3. Because the study was planned after the completion of Study 3SI-GCMN001, data on events occurring before enrollment in this study were collected retrospectively based on medical records (the retrospective study). Hence, the numbers of subjects experiencing adverse events before enrollment (based on the retrospective study) and after enrollment were assessed separately.

The retrospective study revealed adverse events occurring in 7 subjects, and 3 subjects experienced adverse events after enrollment in this study (Table 7-5).

[2] Severity was graded according to the following criteria.
(1) Mild, treatment is not required or normal growth is not affected.
(2) Moderate, treatment is not required but normal growth is affected.
(3) Severe, normal growth is affected and any intervention/treatment is required.

Table 7-5. Adverse events observed in Study J-TEC-GCMN002

Event term	No. of subjects with event based on retrospective study (%)	No. of subjects with event occurring in this study (%)
Infections and infestations	4 (50.0)	3 (37.5)
Bronchitis	0 (0)	1 (12.5)
Empyema	1 (12.5)	0 (0)
Exanthema subitum	1 (12.5)	0 (0)
Influenza	0 (0)	1 (12.5)
Nasopharyngitis	3 (37.5)	3 (37.5)
Parotitis	1 (12.5)	1 (12.5)
Pharyngoconjunctival fever of children	0 (0)	1 (12.5)
Rotavirus infection	0 (0)	1 (12.5)
Respiratory, thoracic and mediastinal disorders	1 (12.5)	1 (12.5)
Cough	0 (0)	1 (12.5)
Rhinorrhoea	0 (0)	1 (12.5)
Oropharyngeal pain	1 (12.5)	0 (0)
Gastrointestinal disorders	1 (12.5)	1 (12.5)
Diarrhoea	1 (12.5)	1 (12.5)
Skin and subcutaneous tissue disorders	5 (62.5)	0 (0)
Dermatitis diaper	1 (12.5)	0 (0)
Hypertrophic scar	3 (37.5)	0 (0)
Pruritus	2 (25.0)	0 (0)
Skin erosion	1 (12.5)	0 (0)
General disorders and administration site conditions	3 (37.5)	1 (12.5)
Pyrexia	3 (37.5)	1 (12.5)
Injury, poisoning and procedural complications	4 (50.0)	1 (12.5)
Laceration	0 (0)	1 (12.5)
Contusion	0 (0)	1 (12.5)
Procedural pain	1 (12.5)	0 (0)
Incision site rash	1 (12.5)	0 (0)
Skin graft scar contracture	3 (37.5)	0 (0)

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A serious adverse event of bronchitis occurred in 1 subject, but its causal relationship to JACE was ruled out. There were no deaths or other serious adverse events.

The retrospective study revealed that adverse events for which a causal relationship to JACE could not be ruled out were hypertrophic scar (3 subjects [H-3, K-1, and T-1]) and skin graft scar contracture (3 subjects [H-2, H-3, and K-1]). According to the severity grading criteria,[3] hypertrophic scar (3 subjects) and skin graft scar contracture (2 subjects [H-2 and H-3) were graded as mild B (these events required treatment), and skin graft scar contracture (1 subject [K-1]) was graded as mild A. A causal relationship to the product was ruled out for all the adverse events occurring after enrollment in Study J-TEC-GCMN002.

Safety was assessed based on the safety assessment criteria. JACE was rated as “very safe” in 4 subjects (K-3,

[3] Severity was graded according to the following criteria.
(1) Mild A, treatment is not required or normal growth is not affected.
(2) Mild B, treatment is not required but normal growth is affected.
(3) Moderate, treatment is not required but normal growth is affected.
(4) Severe, normal growth is affected and any intervention/treatment is required.

K-4, M-1, and M-2) and "not very safe" in 4 subjects (H-2, H-3, K-1, and T-1). "Not very safe" adverse events for which a causal relationship to the product could not be ruled out were all graded as mild A or mild B, and none of those events were severe or moderate.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning of JACE

The applicant's explanation on the intended patient population and clinical positioning of JACE:

Because GCMN, which does not disappear with age, has the potential to develop into malignant melanoma in future, nevus lesions should preferably be excised early in life. (*Plast Reconstr Surg*. 2009; 124 (1 Suppl): 1e-13e). GCMN is treated with a variety of techniques such as excision and suture, serial excision, tissue expansion, skin grafting, laser treatment, and curettage, and they are often combined. A nevus located on the back, for example, covering approximately 1% of the total body surface area, can be treated with these conventional techniques. Larger nevi, however, especially those covering ≥5% of the total body surface area, are difficult to treat with these conventional techniques for the following reasons.

- Excision and suture: Limitation on the size of suturable wound.
- Tissue expansion: Long term effects of excessive excision and suture on skeletal growth and the risks of infection and skin necrosis associated with expander implantation.
- Skin grafting: Lack of sufficient autologous donor skin in infants due to their small body size and scarring at the donor site.
- Laser treatment: Frequent laser irradiation may stimulate nevus cells, thereby making the condition of the lesions even worse.
- Curettage: The use of this minimally invasive technique that requires shorter operation time and less blood loss is limited to neonates and depends on the location and condition of nevi. These limitations preclude complete removal of nevi by this technique alone (*Br J Plast Surg.* 1987; 40: 410-19). After curettage, the wound surface is covered with a dressing, etc. to facilitate epithelialization. Persistent epithelial defect may result in an increased risk of hypertrophic scar or infection or poor exudate management (*Journal of Clinical and Experimental Medicine.* 2011; 238: 867-72).

According to recent reports, cultured epidermal autografts generated with Green's technique were used to treat GCMN and the use of the autografts contributed to early wound healing and less frequent hypertrophic scar and infection. These reports have suggested the benefit of cultured epidermal autografts (*Dermatol Surg*. 2005; 31: 1660-67, *J Burn Care Res*. 2009; 30: 576-86).

The size of skin to be harvested to produce the cultured epidermal cell sheets (i.e., autologous cultured epidermis) is approximately 1 to 2 cm^2. The use of the cultured epidermal cell sheets has an advantage over skin grafting in terms of preserving normal skin, and can offer a new treatment option for patients with a nevus that requires serial excisions. Consequently, the cultured epidermal cell sheets will allow nevus excision in most patients with lesions that are untreatable or very difficult to treat with the conventional techniques.

Based on the above, grafting of the cultured epidermal cell sheets onto a wound after excision of GCMN is

expected to reduce the disadvantages (e.g., the risk of infection or hypertrophic scar) of curettage and other conventional techniques and to minimize the effects on child growth by preventing contracture due to scars, etc. Furthermore, improved color or tone of the lesion area will improve patients' QOL. The use of JACE enables nevus excision in neonates, thus reducing their future risk of malignant melanoma.

PMDA's view:
The applicant's view (grafting of the cultured epidermal cell sheets onto a wound with some dermis remaining after excision of GCMN is expected to promote epithelialization, thus preventing scar contracture and reducing the risk of infection; and the production of the cultured epidermal cell sheets requires a smaller donor site [normal skin] than that for skin grafting) is appropriate. Positioning JACE as a new option for the treatment of wounds after nevus excision is of clinical significance.

On the other hand, the efficacy and safety of JACE used for a nevus excision wound involving loss of dermis were not assessed in the clinical studies. PMDA's conclusion on the use of JACE in such cases and the points to consider is later described in 7.R.5.2.2.

7.R.2 Efficacy of JACE

7.R.2.1 Clinical data package for JACE

The applicant's explanation on the reason for filing a partial change application for approval of the new indication based on the results from Studies 3SI-GCMN001 and J-TEC-GCMN002:
Study 3SI-GCMN001 was intended to assess the efficacy and safety of the cultured epidermal cell sheets used to treat wounds with some dermis remaining after nevus excision. A head-to-head clinical study was infeasible because eligible patients were suffering GCMN that was untreatable or very difficult to treat with conventional techniques. For this reason, the open-label, uncontrolled study design was selected. In Study 3SI-GCMN001, grafting of the cultured epidermal cell sheets onto a wound with dermis preserved after nevus excision promoted rapid epithelialization, resulting in the closure of the wound while posing no safety concerns. In the subsequent Study J-TEC-GCMN002, there were no problems with the long-term safety of the cultured epidermal cell sheets grafted in patients with GCMN. Thus, a clinical data package consisting of the results from these 2 studies was considered appropriate.

PMDA's review policy for evaluation of the efficacy of JACE:
The submitted data only represent a small number of subjects evaluated in open-label, uncontrolled studies. Nevertheless, Study 3SI-GCMN001 showed favorable results, i.e. ≥95% epithelialization achieved in all subjects treated with JACE. Making JACE or autologous cultured epidermis available for clinical use as a new treatment option for wounds after excision of GCMN is of significance. Considering these facts and the rareness of GCMN in Japan, PMDA decided to evaluate the efficacy of JACE based on the results of these 2 studies.

7.R.2.2 Efficacy endpoint

PMDA asked the applicant to explain the appropriateness of the epithelialization rate as the efficacy endpoint for Study 3SI-GCMN001.

The applicant's explanation:

Because grafting of the JACE cultured epidermal cell sheet (autologous cultured epidermis) is expected to promote rapid epithelialization of wounds after nevus excision, epithelialization rate is the appropriate efficacy endpoint. In current clinical practice, patients are discharged when approximately 80% epithelialization is achieved. As seen in Study 3SI-GCMN001, the cultured epidermal cell sheets are engrafted more easily onto a wound with some dermis remaining after excision of nevi. Given these facts, complete epithelialization was defined as "drying up of ≥95% of the graft recipient site."

PMDA's view:

Grafting of autologous cultured epidermis onto a nevus excision wound is known to accelerate epithelialization, thereby resulting in reduced risk of hypertrophic scar, infection, etc. associated with delayed epithelialization (*Dermatol Surg*. 2005; 31: 1660-67, *J Burn Care Res*. 2009; 30: 576-86, etc.). The primary efficacy endpoint of Study 3SI-GCMN001 reflects such clinical significance of JACE and thus is justified. On the other hand, patient characteristics and the sizes of wounds after nevus excision were diverse among subjects treated with JACE in Study 3SI-GCMN001, and these factors are assumed to affect the rates of epithelialization of wounds, time to complete epithelialization, etc. Hence, the significance of the results from Study 3SI-GCMN001 should be assessed on a subject-by-subject basis, considering the results of secondary endpoints as well as achievement of ≥95% epithelialization.

7.R.2.3 Results of efficacy assessment

PMDA asked the applicant to explain the reasons why subjects with larger wounds (4.7%-5.3% of the total body surface area) had a longer time to complete epithelialization in Study 3SI-GCMN001.

The applicant's explanation for each subject:

Subject H-3

At 4 weeks after the initial grafting, the subject was discharged upon confirmation of complete epithelialization. At 5 weeks, however, enlargement of an existing ulcer and formation of a new ulcer in the epithelialized area resulted in a decrease in the epithelialization rate to 82.1%. Then, the assessment of epithelialization was continued until ≥95% re-epithelialization was achieved.

Subject M-1

At 8 weeks after the initial grafting, the subject was discharged upon confirmation of 90.0% epithelialization. At 12 weeks, complete epithelialization was observed. As compared to others, the subject had a more extensive nevus excised and suffered concomitant asteatotic eczema persisting throughout the study period. These factors may have affected the wound healing. In addition, the possibility remains that herpes zoster developing on the left trigeminal territory in the early post-grafting period was also associated with delayed

epithelialization.

Although patients with a nevus covering approximately ≥5% of the total body surface area were eligible for enrollment in Study 3SI-GCMN001, the actual sizes of wounds after nevus excision ranged 1.2% to 5.3% of the total body surface area. Namely, the cultured epidermal cell sheets were grafted on only part of the affected site. PMDA asked the applicant to explain epithelialization of the graft recipient site (epithelialization rate, time to complete epithelialization, etc.) and its clinical significance by classifying the subjects into 2 categories, i.e., those with larger excision wound (H-2, H-3, and M-1; 4.7%-5.3% of the total body surface area) and those with smaller excision wound (K-1, K-3, K-4, M-2, and T-1; 1.2%-2.6% of the total body surface area), while taking account of the current practice in the treatment of GCMN.

The applicant's explanation:
Generally, a nevus covering 1.0% to 1.5% of the total body surface area in infants can be excised in a single procedure. However, in Study 3SI-GCMN001, complete epithelialization was achieved without severe or moderate malfunctions in subjects undergoing the excision of a nevus covering 4.7% to 5.3% of the total body surface area. This result indicates that the use of the cultured epidermal cell sheets enables the excision of an extensive nevus, showing its extremely high clinical significance.

A nevus covering 1.2% to 2.6% of the total body surface area is difficult to be removed in a single-staged excision and suture, and is treated with a series of procedures over several years. However, in Study 3SI-GCMN001, subjects undergoing the excision of a nevus covering 1.2% to 2.6% of the total body surface area achieved epithelialization within 14 days after grafting. The result supports the possibility that grafting of the cultured epidermal cell sheets allows early wound closure, thus reducing postoperative pain, exudates, the risk of postoperative wound infection, etc. JACE is also expected to have advantages such as less frequent operations, a shorter treatment period, and a reduced burden on donor sites than the conventional techniques, and to provide broader treatment options in future.

PMDA's view:
Of 8 subjects who had undergone grafting, 5 achieved complete epithelialization as early as 2 weeks after grafting and required no additional grafting procedures. Despite results from an open-label, uncontrolled study, but the data suggested that the use of JACE may reduce treatment duration including preoperative procedures as compared with the conventional technique (excision and suture or tissue expansion). The remaining 3 subjects underwent the excision of a nevus covering a higher percentage of the total body surface area. Of these, 2 subjects (H-3 and M-1) had a longer time to complete epithelialization, but epithelialization was achieved following additional grafting. Hypertrophic scar at the graft recipient site was mild in severity, and no infection occurred. Taking account of these findings, epithelialization after the grafting of the cultured autologous epidermal cell sheets in these 3 subjects is of clinical significance.

All of the 8 subjects who had undergone the grafting of the cultured autologous epidermal cell sheets in Study

3SI-GCMN001 showed clinically significant complete epithelialization. PMDA concluded that the study demonstrated a certain level of efficacy of JACE.

Subjects H-2 and H-3 achieved complete epithelialization at 4 weeks after the initial grafting (at discharge), but observation and data collection were continued after discharge. PMDA asked the applicant to explain its reason.

The applicant's explanation for each subject:

Subject H-2

The epithelialization rate was 98.1% at 4 weeks after the initial grafting. The subject was discharged on the day following the assessment of epithelialization. The subject was followed up for skin ulcer at the graft recipient site until 37 days after discharge (9 weeks after the initial grafting), and the epithelialization rate was determined as reference data at the last observation.

Subject H-3

The subject was discharged after the epithelialization rate of 95.4% was achieved at 4 weeks after the initial grafting. The follow-up visit at 5 days after discharge for skin ulcer and skin exfoliation revealed enlargement of an existing ulcer and formation of a new ulcer, and the epithelialization rate decreased to 82.1%. Thus, the monitoring was continued until the achievement of ≥95% epithelialization, along with the follow-up for the adverse events.

PMDA's view:

Subject H-3 achieved >95% epithelialization at discharge (24 days after the initial grafting) and the outcome was considered "effective." Therefore, the subject should have been assessed based on the epithelialization rate at discharge and time to epithelialization as per the pre-specified definition. Accordingly, in the efficacy assessment of Subject H-3, the final epithelialization rate should be 95.4% (the rate of epithelialization at 4 weeks after the initial grafting), and the time to complete epithelialization should be 24 days. Given the favorable final epithelialization rate and reference data after discharge, the enlargement of ulcer after discharge in the subject did not pose a problem for the efficacy assessment in Study 3SI-GCMN001.

7.R.3 Safety of JACE

The applicant's explanation on the safety of JACE in Study 3SI-GCMN001:

A serious adverse event (graft recipient site infection) occurred in 1 subject. The event was considered attributable to scratches by the subject during the wound healing process, and its causal relationship to JACE was ruled out. Non-serious, moderate adverse events (pruritus) occurred in 2 subjects. The events were both considered associated with wound healing, and their causal relationship to JACE was ruled out. Other moderate adverse events reported were cellulitis (1 subject), herpes zoster (1 subject), and red rash (1 subject). All of the events occurred in areas other than the graft recipient site, and their causal relationship to JACE was ruled out. A causal relationship to JACE could not be ruled out for ulcer (2 subjects), itching (2 subjects), skin exfoliation (1 subject), erosion at the graft recipient site (1 subject), and extension of non-

epithelialized area (1 subject), but these events were all mild in severity. Furthermore, no neoplastic lesion, allergic symptom, or unknown infection with a possible causal relationship to JACE was observed at the graft recipient site. According to safety assessment based on the safety assessment criteria, JACE was rated as "not very safe" in 3 subjects, but adverse events with a possible causal relationship to JACE occurring in these subjects were all mild in severity. The above results showed that JACE posed no safety problems in patients with GCMN.

PMDA asked the applicant to explain adverse events occurring during the period between skin harvest for the production of cultured autologous epidermal cell sheets and the grafting of the cell sheets.

The applicant's explanation:
There were no abnormalities at donor sites during the period between skin harvest and grafting (or through the date of consent withdrawal for 2 subjects who did not undergo grafting after skin harvest).

PMDA's view:
Ulcer at the graft recipient site in 2 subjects resolved without treatment or with treatment with ointment, itching in 2 subjects resolved with pro-re-nata medication, and extension of non-epithelialized area in 1 subject also resolved without treatment. All of these events were tolerable and similar to events associated with ordinary skin grafting, requiring no particular precautions. On the other hand, skin exfoliation at the graft recipient site was noted in a subject with good epithelialization. This event occurred because a gauze stuck to the grafted cell sheets during treatment after discharge. Such a situation therefore requires attention. However, no additional precautionary advice is required for the present application, because the "Precautions for Dosage and Administration or Method of Use" section of the current package insert of JACE includes the following statements: "The JACE cultured autologous epidermal cell sheets are thin, fragile and sensitive to drying. Mechanical friction and drying should be avoided until engraftment and epithelialization have been completed. The cell sheet graft should be carefully protected and immobilized in an appropriate manner so that they are not displaced or come off." and "The cell sheet graft should be handled carefully for a certain period after grafting."

There are no particular problems with skin harvest for the production of the cultured autologous epidermal cell sheets because no events of safety concern were observed.

The applicant's explanation on the long-term safety of JACE, based on the results of Study J-TEC-GCMN002:
The state of the skin graft after complete epithelialization was evaluated, and no erosion, ulceration, or infection at the graft recipient site was observed at 6 months or 1 year post-grafting. Skin graft scar contracture at the graft recipient site occurred in 3 subjects within 6 months after the initial grafting, but there was no new onset of contracture at >6 months after the initial grafting. These events of skin graft scar contracture were all rated as "contracture that does not impair mobility or affect the surrounding area." Contracture did not resolve completely within 1 year after grafting but tended to soften clearly as compared with the condition at

onset, and all these events were reported as “resolving.” Hypertrophic scar and skin graft scar contracture are also seen after treatment with conventional techniques during the wound healing process after epithelialization. The observed events were all mild in severity and manageable with ordinary treatment. No neoplastic lesions at the graft recipient site or other sites, allergic symptoms, or infection of unknown cause were reported. The results demonstrated no problems with the long-term safety of JACE in patients with GCMN.

PMDA asked the applicant to explain the reasons for the occurrence of skin graft scar contracture in 3 subjects, and compare these subjects with those who did not experience the event.

The applicant’s explanation:
Hypertrophic scar or skin graft scar contracture did not occur in 4 subjects who had undergone grafting of the cultured autologous epidermal cell sheets on their back (K-3, K-4, M-1, and M-2). Generally, the dermis of the back is thicker than that of other sites. Therefore, the occurrence of these events may be associated with the thickness of the preserved dermis. Skin graft scar contracture at sites other than the back may therefore have resulted from scarring at the site of skin ulcer due to a delay in epithelialization in some areas following the occurrence of skin ulcer before complete epithelialization.

PMDA’s view:
Hypertrophic scar is seen even in the wound healing process following the nevus excision with conventional techniques. In the study, hypertrophic scars were resolving after treatment during the observation period and skin graft scar contractures also were resolving after treatment. Given the outcomes, these post-grafting adverse events will not pose any major safety problems. However, because hypertrophic scar or skin graft scar contracture occurred in patients who had a wound after excision of a nevus covering a large portion of the total body surface area and those who experienced skin ulcer, the size of a nevus excised in a single procedure and other precautions should be carefully determined for the use of JACE [see Section 7.R.5.2.2]. No neoplastic lesions, allergic symptoms, or unknown infections were reported during the observation period of Study 3SI-GCMN001 or J-TEC-GCMN002, but data on these events should be further collected.

7.R.4 Indication or performance
The indication or performance proposed in the present application is as follows:

Indication or Performance
2. Giant congenital melanocytic nevi
The cultured epidermal cell sheet is applied onto a wound after excision of giant congenital melanocytic nevi to facilitate the closure of the wound.

The applicant’s explanation on the patient population eligible for treatment with JACE:
Currently available typical treatments for GCMN include serial excision (excision of part of a nevus is repeated at intervals of approximately 6 months), excision + skin grafting, and tissue expansion. A combination of

treatments is determined based on the size and location of the nevus to be excised and the medical institution's therapeutic policy. Generally, a patient can be treated with ≤3 procedures for autografting due to the limited availability of donor skin for autografting. A series of 3 grafting procedures is assumed to allow complete removal of a nevus covering approximately 5% of the total body surface area in adults. Therefore, Study 3SI-GCMN001 enrolled "patients with a nevus covering approximately ≥5% of the total body surface area and requiring ≥4 procedures with conventional techniques," who cannot adequately be treated with conventional techniques.

Based on the above, the patient population eligible for treatment with JACE should be patients with GCMN covering ≥5% of the total body surface area that is untreatable or very difficult to be treated with techniques such as excision, excision + skin grafting, and tissue expansion, alone or in combination.

PMDA's view:

In Study 3SI-GCMN001, 8 subjects underwent the grafting of the JACE cultured autologous epidermal cell sheets onto a wound after nevus excision. Complete epithelialization was achieved in all of the 8 subjects within 12 weeks, demonstrating a certain degree of efficacy of JACE. The safety analysis revealed no adverse events of special concern. GCMN is a rare disease requiring treatment in early infancy, and there exist patients suffering difficult-to-treat GCMN. Taking account of these facts, the proposed indication or performance of "closure of the wound after excision of giant congenital melanocytic nevi" is acceptable. However, according to the applicant, GCMN covering up to approximately 5% of the total body surface area can be treated with conventional techniques. JACE was used in patients with GCMN covering ≥5% of the total body surface area in Study 3SI-GCMN001. Due to no control group, the study failed to demonstrate the advantage of JACE over the conventional techniques. Therefore, JACE should be indicated for use in patients with a nevus covering ≥5% of the total body surface area that is difficult to remove completely with conventional techniques (i.e., the patient population eligible for enrolment in Study 3SI-GCMN001). Thus, the following statement should be included in the "Precautions for Indication or Performance" section of the package insert.

- JACE should be used to treat a nevus that cannot be removed completely with conventional standard techniques, or more specifically, a nevus covering >5% of the total body surface area.

The grafting of the cultured autologous epidermal cell sheets requires nevus excision with a dermatome, etc. to be performed in advance. PMDA asked the applicant to explain whether to specify criteria including the age and size of patients to be treated with JACE, in terms of the feasibility of nevus excision.

The applicant's explanation:

In Study 3SI-GCMN001, the youngest subject who underwent the grafting of the JACE cultured autologous epidermal cell sheets was 7 months of age. All 8 subjects including this subject underwent nevus excision with a dermatome before grafting. The use of cultured epidermal autografts in patients with GCMN aged 1, 2, and 3 months has been reported overseas (*Dermatol Surg*. 2005; 31: 1660-67), showing the feasibility of nevus removal by curettage in patients ≤3 months of age. Limiting age and/or size of patients may cause patients to miss a therapeutic opportunity for a good prognosis, and thus such limitation is unnecessary.

PMDA's view:

While the youngest subject treated with JACE in Study 3SI-GCMN001was 7 months of age, the use of cultured epidermal autografts in a 1-month-old patient has been reported. In the treatment of GCMN, nevi should preferably be excised early in life due to the future risk of malignant melanoma. In light of patient population to be treated with JACE in clinical settings, limiting patient eligibility by age, size, etc., is not necessary. However, post-marketing data on the age and size of patients who have been treated with JACE and the safety of JACE in routine clinical practice should be collected and appropriately provided to healthcare professionals.

Based on the above, the indication or performance should be as follows.

Indication or Performance

2. Giant congenital melanocytic nevi

The cultured epidermal cell sheet is applied onto a wound after excision of giant congenital melanocytic nevi to facilitate the closure of the wound.

Precautions for Indication or Performance

- JACE should be used to treat a nevus that cannot be removed completely with conventional standard techniques, or more specifically, a nevus covering >5% of the total body surface area.

The indication or performance of JACE will be finalized based on comments from the Expert Discussion.

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

7.R.5.1 Tissue harvest

There were no safety problems with skin harvest from healthy donor sites for the production of the cultured autologous epidermal cell sheets (donor site size, approximately 2 cm^2) or the production of cell sheets from the harvested skin in Study 3SI-GCMN001. It is unlikely that donor skin from patients with GCMN will have disadvantages for the production of the cultured autologous epidermal cell sheets as compared with that from patients with severe burns (the approved indication). PMDA concluded that no change or addition to the tissue harvest procedure is required for the present application.

7.R.5.2 Treatment before grafting

7.R.5.2.1 Selection of technique for nevus excision/curettage to be performed before grafting

PMDA asked the applicant to explain the selection of a technique for nevus excision/curettage to be performed before grafting, including the feasibility of grafting after nevus excision/curettage using a technique that was not employed in Study 3SI-GCMN001.

The applicant's explanation:

Because the use of a dermatome allows for uniform and extensive excision of nevi, dermatome excision was selected as the first-line nevus removal technique in Study 3SI-GCMN001 to remove as many nevus cells as

possible and to preserve a deeper layer of the dermis. In the study, the nevus was excised with a dermatome in all subjects treated with JACE. Of these, 2 subjects underwent an additional curettage or excision with a scalpel and scissors to remove some nevi in a marginal area adjacent to healthy skin. A dermatome is a surgical instrument commonly used by plastic surgeons for split-thickness skin graft harvest, etc. and nevus excision with a dermatome is preferable in terms of the proficiency of surgeons or physicians. At the same time, surgical instruments such as a curette, a scalpel, a skin graft knife, scissors are used to remove nevus cells remaining after excision with a dermatome and nevi on marginal areas or flexible regions, which are not suitable for the use of a dermatome. Basically, the use of nevus removal techniques other than those employed in Study 3SI-GCMN001 is not expected, but any technique that allows dermis preservation is acceptable.

PMDA's view:
Study 3SI-GCMN001 employed the standard nevus excision/curettage techniques at study sites, and these techniques are expected to be used in routine clinical practice. Thus, no particular precautionary advice is required on this matter. However, because of very limited clinical experience with the use of JACE to treat wounds after nevus excision, post-marketing data/information should be collected on the relationship of the nevus excision technique selected based on each patient's age and graft recipient site with the efficacy and safety of JACE, and appropriately communicated to healthcare professionals.

7.R.5.2.2 Size (area and depth) of nevus to be excised before grafting and use after dermal reconstruction
PMDA asked the applicant to explain the relationship of the size (area and depth) of a nevus to be excised with a dermatome etc. or removed by curettage before grafting with the efficacy and safety of JACE, including cases requiring dermal reconstruction. Because the protocol of Study 3SI-GCMN001 specified that the size of a nevus to be removed in a single procedure should be ≤15% of the total body surface area, PMDA asked the applicant to explain the method of use of JACE expected to be employed in routine clinical practice, including the graft size.

The applicant's explanation:
In Study 3SI-GCMN001, ≥95% epithelialization was achieved in all of 8 subjects treated with JACE, adverse events for which a causal relationship to JACE could not be ruled out in these subjects were all mild in severity. This indicates no problems with the sizes of excised nevi in the study. Study 3SI-GCMN001 was the first study evaluating the use of JACE in patients with GCMN, and the size of a nevus to be removed in a single procedure had to be ≤15% of the total body surface area to avoid the risk of delayed wound healing due to infection, ulcer, etc. At the same time, given that the primary objective of treatment with JACE in routine clinical practice is to remove extensive GCMN in early infancy and thereby reduce the future risk of malignant melanoma, patient characteristics (nevus size, age, complications, etc.) and the graft recipient site should be taken into consideration before the use of JACE. A nevus that is too large to be excised at a time is inferred to undergo serial excision for treatment with JACE. Thus, the size of a nevus to be removed in a single procedure does not necessarily have to be ≤15% of the total body surface area.

The protocol of Study 3SI-GCMN001 required the preservation of some dermis after nevus excision, but it did not specify the depth of excision because nevi have irregular surfaces which are often elevated. The efficacy and safety of JACE in the treatment of wounds requiring dermal reconstruction were not assessed in Study 3SI-GCMN001. Nevertheless, based on the clinical experience with the use of JACE in patients with severe burns who had undergone dermal reconstruction, the product is expected to demonstrate similar efficacy and safety in patients with GCMN.

PMDA's view:
In Study 3SI-GCMN001, ≥95% epithelialization was achieved in all of 8 subjects treated with JACE while no serious adverse events attributable to the graft recipient site or graft size were reported. Therefore, the feasibility of the grafting was verified in term of the sizes of the nevi excised in Study 3SI-GCMN001. However, the study revealed prolonged time to epithelialization in 3 subjects with a higher percentage of the total body surface area involved in nevus excision. Of these, 2 subjects (H-2 and H-3) had skin graft scar contracture and 1 subject (H-3) had hypertrophic scar. Information on the size of the nevus excised in a single procedure before grafting should be therefore provided based on the results from Study 3SI-GCMN001. Accordingly, the size of the nevus excised before grafting is to be explained in the "Clinical Studies" section of the package insert based on the results of Study 3SI-GCMN001.

None of the patients with GCMN treated with JACE required dermal reconstruction before grafting. On the other hand, JACE was used in some patients with severe burns who underwent dermal reconstruction before grafting. In light of the condition of nevus excision wounds, GCMN is unlikely to be disadvantageous in epithelialization as compared to severe burns. The JACE cultured autologous epidermal cell sheet is expected to be engrafted on the reconstructed dermis of wounds after excision of GCMN by a mechanism similar to that for severe burns. Therefore, the cultured epidermal cell sheets can be used on wounds after nevus excision followed by dermal reconstruction. Thus, the "Dosage and Administration or Method of Use" section of the package insert can include advice to the effect that dermal reconstruction should precede the grafting of the cultured epidermal cell sheets as needed for patients with GCMN. Such advice is acceptable.

Post-marketing data on the size (area and depth) of a nevus to be removed by excision or curettage before grafting and a history of dermal reconstruction should be collected to assess the association of these patient characteristics with the efficacy and safety of JACE.

7.R.5.3 Number of the cultured autologous epidermal cell sheets to be grafted in a single procedure and total number of cell sheets to be grafted in serial procedures

PMDA asked the applicant to explain whether precautionary advice should be given on the number of the cultured epidermal cell sheets used in a single grafting procedure and the total number of cell sheets used in serial procedures, in light of the fact that children with GCMN are the main patient population for the treatment with JACE.

The applicant's explanation:

The maximum number of the cultured epidermal cell sheets to be used in a single grafting procedure or in serial procedures was determined from the standpoint of the safety of residual process-related impurities. Experience with the use of JACE in children with severe burns was also taken into consideration. In Study 3SI-GCMN001, the average number of sheets grafted was 4.5 and the maximum number of sheets grafted was 10 in the initial grafting, and the average number of sheets grafted was 2 and the maximum number of sheets grafted was 4 in the additional grafting. Given these, the number of sheets required for grafting in patients with GCMN is very unlikely to exceed the maximum number of sheets specified in the current package insert. No additional advice is necessary on the number of the cultured epidermal cell sheets required in a single procedure and the total number of sheets required in serial procedures.

PMDA's view:
The applicant's explanation on the number of sheets required in a single grafting procedure and the total number of sheets required in serial grafting procedures is acceptable as long as the lack of clinical experience with the use of ≥15 sheets grafted onto wounds after a single procedure for nevus excision in patients with GCMN is highlighted in the "Clinical Studies" section of the package insert. Some patients may require a series of nevus excision each followed by grafting. Data on the safety, etc. of JACE should be collected from such patients by graft recipient site.

The dosage and administration or method of use for JACE will be finalized, taking account of comments from the Expert Discussion.

7.R.6 Qualifications of medical institutions and surgeons/physicians for using JACE
GCMN is a rare disease, and this indicates the limited availability of surgeons/physicians with experience in treating GCMN. PMDA asked the applicant to explain the requirements for medical institutions and surgeons/physicians to handle JACE properly after the market launch.

The applicant's explanation:
The treatment with JACE involves nevus removal with a dermatome etc. or by curettage, dermal reconstruction, and other techniques. JACE should be appropriately handled by plastic surgeons or dermatologists with adequate knowledge, skills, and experience in surgical treatment of GCMN. Information and training for the proper use of JACE will be provided to surgeons with no relevant experience.

Further, medical institutions are required to have facilities for postoperative management.

PMDA's view:
Given that JACE is used by the specialists and at medical institutions meeting the above-mentioned requirements, they should be provided with information and training through written materials etc., on the nature of JACE, grafting procedure, treatment before and after grafting, precautions for use, etc.

The qualifications of surgeons/physicians and medical institutions and other necessary information to

be communicated to them for the proper use of JACE, etc. will be finalized, taking account of comments from the Expert Discussion.

8. Risk Analysis

The applicant's explanation on a post-marketing use-results survey of JACE:

A post-marketing use-results survey is being planned in patients with GCMN treated with JACE to assess the safety, etc. of the product in clinical use. The survey is intended to include all patients who undergo tissue harvest for the production of the cultured epidermal cell sheets during the re-examination period. The observation period will begin at the time of tissue harvest and end at 52 weeks after the last grafting. This survey duration was determined based on the results of Study J-TEC-GCMN002. In the study, the skin at the graft recipient site after complete epithelialization reached an almost steady state at 6 months after the initial grafting, erosion/ulceration or infection at the graft recipient site was not observed at 6 months or 1 year after the initial grafting, and the observed scar contractures improved by 1 year after the initial grafting and tended to soften over time.

Survey items are patient characteristics, safety, and efficacy. Key survey items are erosion/ulcer, infection, and scar contracture at the graft recipient site; malignant melanoma; and neoplastic lesions at the graft recipient site, allergic symptoms, and infections for which a causal relationship to JACE cannot be ruled out. Data on the development of malignant melanoma at or around the graft recipient site and the tumorigenic risk of the product itself will be further collected even after the completion of the use-results survey, in accordance with "Ministerial Ordinance on Good Vigilance Practice (GVP) for Drugs, Quasi-Drugs, Cosmetics, Medical Devices, and Regenerative Medical Products" (MHLW Ordinance No. 135 dated September 22, 2004).

8.R Outline of the review conducted by PMDA

PMDA's view on a post-marketing use-results survey of JACE:

Based on the post-procedural clinical course of patients treated with JACE in Studies 3SI-GCMN001 and J-TEC-GCMN002, the proposed observation period of 52 weeks after the last grafting is appropriate. However, patients undergoing serial excision of a nevus and subsequent grafting should be followed for 52 weeks after the last grafting for each recipient site. Key survey items should include serious skin lesions at the graft recipient site other than erosion/ulcer, infection, and scar contracture, in addition to those proposed by the applicant. Survey items should include the technique used for nevus excision before grafting, the size (area and depth) of a nevus to be removed by excision or curettage, and dermal reconstruction. Data on these items should be collected so as to assess a relationship between these items and the efficacy and safety of JACE.

Because of very limited safety data of the JACE cultured epidermal cell sheets grafted onto a wound after nevus excision in patients with GCMN, safety information from the post-marketing use-results survey should be provided to healthcare professionals appropriately when it becomes available. At the same time, further safety measures or any appropriate and prompt actions should be taken as needed.

The details of the post-marketing use-results survey will be finalized, taking also account of comments on

efficacy and safety assessment of JACE from the Expert Discussion.

9. Results of Compliance Assessment Concerning the 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 inspection and assessment are currently ongoing. The results and PMDA's conclusion will be reported in the Review Report (2).

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

The inspection is currently ongoing. The results and PMDA's conclusion will be reported in the Review Report (2).

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

PMDA has concluded that the data submitted demonstrate a certain level of efficacy of the cultured autologous epidermal cell sheets grafted onto a wound after nevus excision in patients with GCMN and acceptable safety in view of the benefits indicated by the data submitted. Making JACE available for clinical use as a new option for the treatment of GCMN is of significance.

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

Review Report (2)

September 1, 2016

Product Submitted for Approval

Brand Name	JACE
Non-proprietary Name	Human (autologous) epidermal cell sheet
Applicant	Japan Tissue Engineering Co., Ltd. (J-TEC)
Date of Application	January 29, 2016

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 in the following. 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

An investigator-initiated Japanese clinical study (Study 3SI-GCMN001) was conducted to assess the efficacy and safety of JACE used to treat a wound after nevus excision in patients with giant congenital melanocytic nevus (GCMN) that was untreatable or very difficult to treat with conventional techniques. Clinically significant complete epithelialization was observed in all of 8 subjects who had undergone the grafting of the JACE cultured autologous epidermal cell sheets. Thus, PMDA has concluded that a certain level of efficacy of JACE was demonstrated [see Section 7.R.2 in Review Report (1)].

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.2 Safety

Based on the results from Study 3SI-GCMN001 and a follow-up study in patients treated with JACE in Study 3SI-GCMN001 (Study J-TEC-GCMN002), PMDA considered that patients should be closely monitored for ulcer, itching, skin exfoliation, erosion at the graft recipient site, and extension of non-epithelialized area after the grafting of the cultured human epidermal cell sheets, and that hypertrophic scar and skin graft scar contracture also require attention to evaluate the long-term safety of JACE [see Section 7.R.3 in Review Report (1)]. PMDA has concluded that these events are tolerable and JACE is used by a plastic surgeon or dermatologist with adequate knowledge, skills, and experience in surgical treatment for GCMN at the medical institution to which they belong.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA. PMDA has

also concluded that guidelines for the proper use of JACE will not be necessary. Because of the following reasons, JACE is expected to be used properly in the treatment of GCMN by surgeons/physicians at medical institutions without such guidelines in an established environment.

- JACE has been designated as an orphan regenerative medical product for the claimed indication or performance. Presumably, treatment with JACE will be available only at 70 to 100 medical institutions across Japan. They must have deep experience in treating GCMN with conventional techniques, e.g., skin grafting and nevus excision/curettage.
- JACE is expected to be used by plastic surgeons or dermatologists with adequate experience in treating GCMN belonging to any of the above-mentioned competent medical institutions where adequate follow-up including postoperative wound management can be performed.

1.3 Indication or performance

In light of the results from Studies 3SI-GCMN001 and J-TEC-GCMN002 and the clinical positioning of JACE, the proposed indication or performance of "closure of the wound after excision of giant congenital melanocytic nevi" is acceptable. Meanwhile, the applicant explained that GCMN covering up to approximately 5% of the total body surface area can be treated with the conventional techniques. JACE was used in patients with GCMN covering ≥5% of the total body surface area in Study 3SI-GCMN001, and the study failed to demonstrate the advantage of JACE compared to the conventional techniques due to no control group. Therefore, JACE should be indicated for use in patients with a nevus covering ≥5% of the total body surface area that cannot be removed completely with conventional techniques (i.e. the study population for 3SI-GCMN001). Thus, the following statement should be included in the "Precautions for Indication or Performance" section of the package insert [see Section 7.R.4 in Review Report (1)].

- JACE should be used a nevus that cannot be removed completely with conventional standard techniques, or more specifically, a nevus covering >5% of the total body surface area.

At the Expert Discussion, the expert advisors largely supported the above conclusion by PMDA. At the same time, they expressed the following opinion about the wording of "a nevus cannot be removed completely" in the "Precautions for Indication or Performance" section: Neurocutaneous melanosis (NCM), for example, is characterized by the presence of nevomelanocytes in the central nervous system, and nevi in patients with NCM may not be removed completely even with the use of JACE. In response to this comment, PMDA sought the expert advisors' comments on patients who have a nevus that cannot be removed with conventional standard techniques and who are considered eligible for treatment with JACE, based on current treatment practice for GCMN, and further discussed.

Conventional standard techniques for the treatment of GCMN include excision and suture, serial excision, tissue expansion, skin grafting, laser treatment, and curettage. Known disadvantages of these techniques include limitations on the size of a nevus to be excised, surgical invasion, limited availability of donor skin, scarring of donor skin sites, and postoperative complications (*Rinsho derma*. 2002; 44: 513-17, *An Bras Dermatol*. 2013; 88: 863-73, etc.). In a clinical study on cultured epidermal autografts grafted onto a wound

after nevus excision, earlier epithelialization with fewer scars and other complications was achieved in subjects who had underdone the grafting than in those who had not (*Dermatol Surg*. 2005; 31: 1660-67). Meanwhile, there are no available data from a head-to-head study of JACE and non-grafting procedures or conventional treatment, and the degree of the effect of JACE on time to epithelialization, scarring, etc. are unclear. Thus, whether to use standard treatment for GCMN should be carefully considered on a patient-by-patient basis before deciding to use JACE. To make this point clear, the "Precautions for Indication or Performance" section of the package insert should include relevant information and precautionary advice to be given prior to the use of JACE based on the experience in Study 3SI-GCMN001.

Based on the above, PMDA has concluded that the indication or performance and precautions for indication or performance should be as shown below.

Indication or Performance

2. Giant congenital melanocytic nevi

The cultured epidermal cell sheet is applied onto a wound after excision of giant congenital melanocytic nevi to facilitate the closure of the wound.

Precautions for Indication or Performance

- JACE should be used to treat a nevus that cannot be removed completely with conventional standard techniques, or more specifically, a nevus covering ≥5% of the total body surface area.

PMDA instructed the applicant to modify the "Indication or Performance" and "Precautions for Indication or Performance" sections of the package insert as shown above.

1.4 Dosage and administration or method of use

Based on the results of Study 3SI-GCMN001, PMDA has concluded that dosage and administration or method of use for JACE should be described as below [see Section 7.R.5 in Review Report (1)].

- No change or addition to the tissue harvest procedure for the production of JACE is required for the proposed additional indication.
- No particular precautionary advice is required on the selection of a technique for nevus removal before grafting. Study 3SI-GCMN001 employed nevus excision and curettage that are common in clinical practice, and those techniques posed no problems.
- The feasibility of treatment with JACE was demonstrated based on the sizes of nevi actually excised in Study 3SI-GCMN001. Relevant data from Study 3SI-GCMN001 should be included in the "Clinical Studies" section of the package insert.
- There is no clinical experience with the use of JACE after dermal reconstruction in patients with GCMN. However, based on the experience with the use of JACE in the treatment for severe burns, etc., the product may also be used on the reconstructed dermis to treat nevus excision wounds as appropriate.
- Precautionary advice on the number of the cultured epidermal cell sheets to be grafted in a single procedure

and the total number of sheets to be grafted in serial procedures was provided in the package insert at approval of JACE for severe burns. The number of sheets required for grafting in patients with GCMN is very unlikely to exceed the maximum number of sheets specified for the treatment of severe burns. Thus, no new precautionary advice is required for GCMN.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA. Therefore, PMDA instructed the applicant to appropriately include the above information in the "Clinical Studies" section of the package insert.

1.5 Post-marketing use-results survey plan (draft)

Because of very limited data on the safety of JACE used for grafting, PMDA concluded that a post-marketing use-results survey that assesses the safety, etc. of JACE in clinical settings should be designed and conducted in light of the following points [see "8. Risk Analysis"in Review Report (1),].

- All patients treated with JACE during the re-examination period should be surveyed.
- The proposed observation period of 52 weeks after the last grafting is appropriate. In Study J-TEC-GCMN002, erosion/ulceration or infection at the graft recipient site did not occur at 6 months or 1 year after the initial grafting. The observed scar contractures was resolving by 1 year after the initial grafting and tended to soften over time. However, patients undergoing serial excision of a nevus and subsequent grafting should be followed for 52 weeks after the last grafting for each recipient site.
- Key survey items should include serious skin lesions at the graft recipient site other than erosion/ulcer, infection, and scar contracture, in addition to those proposed by the applicant at the time of submission (erosion/ulcer, infection, and scar contracture at the graft recipient site; malignant melanoma; and neoplastic lesions at the graft recipient site, allergic symptoms, and infections for which a causal relationship to JACE cannot be ruled out).
- Survey items should include the technique for nevus excision performed before grafting, the size (area and depth) of a nevus to be removed by excision or curettage, and dermal reconstruction, in addition to patient characteristics proposed by the applicant at the time of submission.
- Safety data obtained from the use-results survey should be provided to healthcare professionals accordingly, and further safety measures or other appropriate and prompt actions should be taken as needed.

At the Expert Discussion, the expert advisors largely supported the above conclusion of PMDA. They also expressed their opinions that hypertrophic scar at the graft recipient site should be added to key survey items and that the following should be added to survey items: the presence or absence of concurrent neurocutaneous melanosis, a history of nevus treatment using JACE, the development of nevi at the site treated with JACE, and the reason for the decision to cancel grafting after tissue harvest for the production of the cultured autologous epidermal cell sheets.

Malignant melanoma, one of the safety items, is known to occur secondarily to the primary disease and

generally takes several years to develop. The observation period of 52 weeks are too short to follow up tumor development attributable to the grafting of the JACE cultured autologous epidermal cell sheets. However, JACE is a product consisting of autologous keratinocytes that are not genetically engineered and is unlikely to pose a risk of long-term tumorigenicity of the grafted cells; and no tumor development attributable to JACE was reported during the re-examination period for severe burns, indicating no particular concern about the risk of tumorigenicity. Thus, the proposed 52-week observation period of the use-results survey is acceptable because its primary objective is to assess the safety of JACE used for wound healing after nevus excision over a specified period of time. Data collection will be continued after the completion of the use-results survey, in accordance with "Ministerial Ordinance on Good Vigilance Practice (GVP) for Drugs, Quasi-Drugs, Cosmetics, Medical Devices, and Regenerative Medical Products" (MHLW Ordinance No. 135 dated September 22, 2004), and it is also possible to detect events such as tumor development in the long-term course after grafting.

Taking account of the comments from the Expert Discussion, PMDA asked the applicant to review the post-marketing use-results survey plan. The applicant presented an outline of the modified use-results survey plan (draft) shown in Table 8, and PMDA accepted it.

PMDA concluded that because of the very limited number of subjects enrolled in clinical studies, the use-results survey covering all patients treated with JACE should be conducted until the end of the re-examination period as a rule (the expected number of patients treated with JACE after the market launch [approximately 10-20 patients/year]) and that whether to review the survey period should be determined as appropriate, based on patient enrollment in the survey and the results of periodic interim survey of the safety etc. of JACE.

Table 8. Outline of post-marketing use-results survey (draft)

Objective	To assess the safety etc. of JACE in clinical use
Survey method	All-case surveillance
Population	Patients with GCMN
Observation period	52 weeks after the last grafting for each recipient site
Planned number of patients	All patients who underwent tissue harvest for the production of cultured autologous epidermal cell sheets during the re-examination period
Main survey items	1) Key survey items (1) Erosion/ulcer at the graft recipient site (2) Infection at the graft recipient site (3) Hypertrophic scar at the graft recipient site (4) Scar contracture at the graft recipient site (5) Serious skin lesions at the graft recipient site other than erosion/ulcer, infection, hypertrophic scar, and scar contracture (6) Malignant melanoma (7) Neoplastic lesions at the graft recipient site for which a causal relationship to JACE cannot be ruled out (8) Allergic symptoms for which a causal relationship to JACE cannot be ruled out (9) Infections for which a causal relationship to JACE cannot be ruled out 2) Other survey items (1) Patient characteristics (including the concurrent neurocutaneous melanosis status and a history of nevus treatment with JACE) (2) Surgical technique for nevus excision performed before grafting (3) Size (area and depth) of a nevus removed by excision or curettage (4) A history of dermal reconstruction (5) Development of nevi at the graft recipient site (6) Reason why grafting was not performed after skin tissue harvest for production of JACE

2. Results of Compliance Assessment Concerning the Application Data and Conclusion Reached by PMDA

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

The 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 Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The application data (Attachments 1 and 2) were subjected to an on-site GCP[4] inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication or performance and dosage and administration or method of use shown below, with the following conditions. The product was designated as an orphan regenerative medical product for the claimed indication or performance, and the re-examination period for the indication or performance claimed in the present application is 10 years.

Indication or Performance

1. Severe burns

JACE is indicated for use in patients with serious, extensive burns when sufficient donor sites for autologous skin grafts are not available and the total area of deep dermal and full-thickness burns is 30% or more of the total body surface area. A cultured epidermal cell sheet is applied onto the reconstructed dermis in a full-thickness burn wound to facilitate the closure of the wound. Dermis should be reconstructed with allografts, as a general rule. JACE should be used for deep dermal burn wounds only when full-thickness and deep dermal burns coexist and it is difficult to treat them separately.

2. Giant congenital melanocytic nevi

The cultured epidermal cell sheet is applied onto a wound after excision of giant congenital melanocytic nevi to facilitate the closure of the wound.

(Underline denotes additions.)

Dosage and Administration or Method of Use

[4] Although the present application was filed under the category of regenerative medical products, the clinical studies were conducted before the enforcement of the Ministerial Ordinance on GCP for Regenerative Medical Products. Therefore, the Ministerial Ordinance on GCP for Medical Devices was applicable to these clinical studies.

Grafting plan

1. Grafting plan

A treating surgeon/physician develops a grafting plan and provides the manufacturer of JACE with the details of the plan, which consist of the number of cultured epidermal cell sheets required, the dates of tissue harvest and grafting, the number of grafting procedures, and other necessary information such as on the medical institution and the patient (hereinafter collectively referred to as the "grafting planning information"). The manufacturer prepares an order form indicating a tissue code unique to each grafting plan and the grafting planning information, then send it to the treating surgeon/physician.

The treating surgeon/physician confirms the grafting planning information entered in the order form sent by the manufacturer, before placing an order for production of JACE.

The manufacturer supplies the surgeon/physician with a tissue transport kit (comprising tissue transport tubes) and a dedicated heat-insulating container in time for the date of tissue harvest. The tissue code is indicated on the carton containing the tissue transport kit, tissue transport tubes, and heat-insulating container for tissue transportation provided by the manufacturer.

Tissue code

Tissue code is issued for each grafting plan.

For a patient undergoing tissue harvest more than once, each piece of tissue harvested is identified by a unique tissue code. A grafting plan is developed on a tissue-code basis.

For a patient undergoing a single tissue harvest followed by serial grafting procedures, cultured epidermal cell sheets for multiple grafting procedures are produced using cells derived from the same skin tissue. The tissue code remains unchanged for production of such sheets. Therefore, these sheets are identified with the same tissue code and different batch numbers.

Steps from tissue harvest at the medical institution through the receipt of harvested tissue

2. Tissue harvest

Skin tissue is harvested based on the size of the graft recipient site and according to the grafting plan. The harvested skin should be at least 1 cm^2 in size and elliptical in shape or in such a shape that allows for easier suture. Skin tissue is taken from lesion-free normal skin at any anatomical site. The full-thickness of dermis should be harvested from the donor site.

3. Storage of harvested tissue

The sealing band on the heat-insulating container is cut with scissors to remove the lid and take out the tissue transport kit. The tissue code indicated on the heat-insulating container, carton of the tissue transport kit, and tissue transport tubes is checked against the order form.

The tissue transport kit is unsealed in a clean environment (e.g., operating room, procedure room) to take out the tissue transport tube. The tube is checked for leakage and turbidity of the medium filled in it. If the medium is turbid, the spare tube is used.

The tissue transport tube should not be tilted or shaken unnecessarily.

The tissue transport tube is uncapped. The skin tissue, harvested in a clean environment, is placed in the tube using sterile forceps, etc. to be immersed in the medium. The tube is then capped tightly to prevent a leak of the medium. The date of tissue harvest and the name of the person who performed harvest are indicated on the tube.

4. Transportation of harvested tissue

The tissue transport tube is placed in the carton. The carton is sealed for tamper resistance and placed in the heat-insulating container (temperature during transportation, 4°C to 25°C). The container is sealed with 4 sealing bands for delivery to the manufacturer. The manufacturer should receive the skin tissue within 62 hours after the heat-insulating container has been shipped to the medical institution [see "1. Grafting plan"].

Note: Presumably, each medical institution will follow its own procedure for handling harvested skin tissue and JACE (e.g., special procedures, responsible department). Therefore, the distributor will undertake the transportation of harvested skin tissue and JACE under the supervision of the manufacturer until a reliable system is established and maintained for the delivery and acceptance of harvested skin tissue and JACE. Once such a system is fully in place, part of the transportation process will be outsourced to a logistics company while the distributor will still be responsible for the rest of the process.

Steps from release at the manufacturer through acceptance at the medical institution

5. Acceptance inspection and handling of the product at the medical institution

(1) A package of cultured epidermis is shipped in a heat-insulating container sealed with bands. The medical institution must ensure that the container is kept sealed before use.

The heat-insulating container is unpacked by cutting the sealing band with scissors to take out the package of cultured epidermis.

(2) The tissue code (5-digit alphanumeric code) incorporated in the batch number on the package is checked against the order form retained at the medical institution (issued in the step as described in "1. Grafting plan"). The number of the cultured epidermal cell sheets is checked.

(3) The package of cultured epidermis is stored at 10°C to 25°C until immediately before use.

Grafting

6. Procedures before grafting of the cultured epidermal cell sheet

(1) Severe burns

Dermal reconstruction is performed on the site to be treated with the cultured epidermal cell sheet.

(2) Giant congenital melanocytic nevi

The lesion (nevus) is excised. The surgical technique for excision is determined according to the patient's age and nevus size. Dermal reconstruction is performed as necessary.

7. Grafting of cultured epidermal cell sheet

(1) Severe burns

The cultured epidermal cell sheet is applied onto the reconstructed dermis. However, the grafting should be preceded by appropriate wound bed preparation such as the removal of necrotic tissue or other factors that render the recipient wound bed unsuitable for grafting, if any. The cultured epidermal cell sheet may be used on a deep dermal burn wound only when full-thickness and deep dermal burns coexist and it is difficult to treat them separately.

(2) Giant congenital melanocytic nevi

The cultured epidermal cell sheet is applied onto the preserved dermis or reconstructed dermis of a wound after nevus excision.

8. The number of sheets to be grafted in a single procedure or serial procedures

Up to 50 pieces of cultured epidermal cell sheets are allowed be grafted in a single procedure, and a total of up to 200 cell sheets in serial procedures. The number of cultured epidermal cell sheets used should not exceed these upper limits.

(Underline denotes additions/changes.)

Conditions of Approval

1. Because the clinical studies were conducted in extremely limited number of subjects, the applicant is required to conduct a use-results survey covering all patients treated with the product. As a rule, the survey should be continued until the end of the re-examination period. New efficacy and safety data on the product should be communicated appropriately to surgeon/physicians and medical institutions providing treatment with the product, and patient information materials should be updated with the data accordingly.
2. Due to the risks associated with xenotransplantation of 3T3-J2 cells derived from mouse embryo, which are used as feeder cells in the manufacture of the product, the applicant is required to take necessary measures to ensure appropriate handling, such as 30-year retention of a sample of the finished product and a record of use.