April 18, 2025
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Human Cellular/Tissue-based Products 1. Human Somatic Cell-processed Products
Non-proprietary Name	Human (autologous) cartilage-derived tissue
Brand Name	JACC
Applicant	Japan Tissue Engineering Co., Ltd.
Date of Application	June 17, 2024 (Application for partial change approval)

Results of Deliberation

In its meeting held on April 18, 2025, the Committee on Regenerative Medicine Products and Biotechnology reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Council.

The product may be approved. The re-examination period is 4 years.

The following approval conditions should be attached.

Approval Conditions

1. The applicant is required to take necessary measures, such as disseminating the guidelines for proper use jointly prepared with relevant academic societies and offering seminars, to ensure that the product is used for eligible patients selected, by physicians and at medical institutions with adequate knowledge and experience in the treatment of knee osteoarthritis and a good understanding of the product's efficacy and safety.
2. Because of the extremely limited number of the clinical study participants, the applicant is required to conduct a use-results survey covering all patients treated with the product, until the end of the re-examination period in principle, to understand the characteristics of patients treated with the product, collect product safety/efficacy data promptly, and take necessary measures to ensure its proper use.

Review Report

March 28, 2025
Pharmaceuticals and Medical Devices Agency

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

Brand Name	JACC
Classification	Human Cellular/Tissue-based Products 1. Human Somatic Cell-processed Products
Non-proprietary Name	Human (autologous) cartilage-derived tissue
Applicant	Japan Tissue Engineering Co., Ltd.
Date of Application	June 17, 2024

Shape, Structure, Active Ingredients, Quantities, or Definition

JACC is a regenerative medical product. Its primary component is a cultured cartilage package, coming with the secondary components including atelocollagen for intradermal test, a tissue transport set, a JACC template(s), and a JACC collagen patch(es). The cultured cartilage in the package, the primary component, is "autologous cultured cartilage" that is prepared from chondrocytes isolated from patient's own cartilage tissue and embedded in atelocollagen gel for culturing.

The atelocollagen for intradermal test, a secondary component, is used to test a potential for allergy to bovine dermis-derived collagen.

The tissue transport set, a secondary component consisting of a tissue transport tube and a blood storage tube, is used to store and transport harvested tissue.

The JACC template, a secondary component, is used to shape the recipient site and trim the JACC collagen patch, periosteal patch, and cultured cartilage.

The JACC collagen patch, a secondary component, is used to fix the cultured cartilage transplanted to the recipient site.

Application Classification	(3) Regenerative medical product with a new indication
Reviewing Office	Office of Cellular and Tissue-based Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of knee osteoarthritis, and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indications or Performance

1. Traumatic cartilage defects or osteochondritis dissecans

   Alleviation of clinical symptoms of traumatic cartilage defects or osteochondritis dissecans of the knee exclusively with a cartilage defect measuring 4 cm^2 or larger for which there are no other treatment options

2. Knee osteoarthritis

   Improvement of clinical symptoms of knee osteoarthritis exclusively with a cartilage defect measuring 2 cm^2 or larger which do not respond to exercise therapy or other conservative therapies

(Underline denotes additions.)

Dosage and Administration or Method of Use

1. Transplantation planning
   (1) The marketing authorization holder sends the designated form to the treating physician upon request.
   (2) The treating physician performs pre-procedural testing, namely, beef allergy test for allergy to bovine serum and atelocollagen intradermal test for allergy to bovine dermis-derived collagen. The intradermal test is performed at least 4 weeks prior to transplantation of cultured cartilage (see 2. Intradermal test). If the result of the beef allergy or intradermal test turns out positive, the patient is ineligible for the use of the cultured cartilage, and the cultured cartilage must not be transplanted. Judgment method: the patient is instructed to carefully observe the test site for 4 weeks and report any abnormal reaction during this period. If adverse events or unexpected unknown abnormal reactions such as swelling, redness, itchy feeling, induration, and pyrexia occur, the result of the intradermal test is determined to be positive.
   (3) In the designated form, the treating physician fills in necessary information including the number of cultured cartilage required and dates of tissue harvest and transplantation scheduled, and requests the production of JACC.
   (4) Up to 2 pieces each of JACC templates and JACC collagen patches are packed in one package depending on the necessary number of cultured cartilage, recipient site, shape of the recipient site, etc.
   (5) A patient-specific code is issued for each transplantation plan for identification.

2. Intradermal test (at least 4 weeks prior to the transplantation of cultured cartilage)

(1) Open the package of atelocollagen for intradermal test. Take out the package content, holding the glass syringe with fingers.
(2) Remove the rubber stopper, and securely screw the injection needle into the Luer-lock.
(3) Remove the injection needle cap by pulling it straight out so that the needle tip is not damaged.
(4) Push the plunger slowly to inject approximately 0.1 mL of atelocollagen into the forearm subcutaneously.

3. Sending the tissue transport set

The manufacturer sends the tissue transport set to the medical institution for tissue harvest. The set consists of a tissue transport tube and a blood storage tube. Harvested tissue is stored in a special heat-insulated container for transportation.

4. Tissue harvest

Healthy cartilage tissue must be harvested from the knee joint. The treating physician arthroscopically determines the harvest site where there is no risk of functional impairment after harvest, such as a non-weight-bearing site in the femoral medial or lateral condyle, according to the standard arthroscopic procedure. Tissue is harvested from the superficial to deep layers of the cartilage using a grooved chisel, ring curette, etc. for ear operation with a 3 to 7 mm blade. Approximately 0.4 g of cartilage tissue is harvested. A loose body in the joint must not be harvested.

5. Storage of harvested tissue at medical institution

(1) Open the outer box of the tissue transport tube in a clean environment (e.g., surgical room and treatment room). Check the tissue transport tube for leakage and turbidity of the tissue transport liquid in the tube. The tube should not be tilted or shaken excessively.
(2) Uncap the tissue transport tube. In a clean environment, bring the harvested cartilage tissue using sterile tweezers, etc. to be immersed in the tissue transport liquid in the tube. Cap the tube tightly to prevent a leak of the liquid.
(3) Collect blood according to the standard procedure. Store the collected blood in the blood storage tube.
(4) To prevent mix-up, label the tissue transport tube, blood storage tube, and the designated form with the patient-specific code.

6. Transportation of harvested tissue

The tissue transport tube and blood storage tube containing the collected blood are placed back into the outer box, which is then sealed with a sticker and placed in the heat-insulated transport container. The container is sealed at 4 spots with sealing bands and sent back to the manufacturer (transport temperature, 2°C-20°C). The expiration date (the duration for temperature control capability), which is clearly indicated on the heat-insulated transport container provided by the manufacturer, must be strictly observed.

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

(1) The package of cultured cartilage is transported in a heat-insulated transport container sealed with sealing bands. Upon the arrival of the package, the medical institution must ensure that the heat-insulated transport container is sealed. If the sealing is broken, the package should not be opened, and the medical institution should contact the marketing authorization holder.
(2) Cut the sealing bands of the heat-insulated transport container and take out the package of cultured cartilage.
(3) Cross-check the tissue code on the transport container against the designated form kept at the medical institution, and check the quantity of the contents.
(4) Visually check the transport container for cracks, chips, and leakage, and turbidity and foreign matters in the transport liquid. Store at 8°C to 25°C until immediately before use. If any of these abnormalities is identified, the cultured cartilage must not be used.
(5) The cultured cartilage should be transplanted before the expiration date written on the transport container. Expired products must not be used.

8. Pre-transplantation check

Take out the multipurpose dish, with the cultured cartilage on it, from the transport container and place it in a clean area. When taking out the cultured cartilage from the container, double-check the transport liquid for turbidity or foreign matters. Cultured cartilage must not be used in case the transport liquid is turbid or contaminated.

9. Transplantation procedure (example)

(1) Expose the defect site according to the standard surgical procedure.
(2) Debride the degenerative cartilage, etc. at the defect site to expose the subchondral bone.
(3) Debride the degenerative cartilage, etc. around the defect site so that the recipient site is clear.
(4) Shape the JACC template, etc. as necessary to fit the recipient site.
(5) Place a fixation patch (either the JACC collagen patch or periosteal patch) over the recipient site to anchor the cultured cartilage according to the following procedures:
    1) With JACC collagen patch
    Cut the JACC collagen patch into the shape and size of the shaped JACC template, etc. and immerse the patch in Ringer's solution, physiological saline, etc., allowing it to swell. Place the JACC collagen patch over the recipient site with its porous surface on the bone side.
    2) With Periosteal patch
    From the surface of the proximal anteromedial tibia, harvest a periosteal patch in a size slightly larger than the shaped JACC template, etc. Place the patch over the recipient site with its osteogenetic layer touching the joint surface.
(6) Suture the fixation patch halfway around the perimeter to the surrounding cartilage. Stitches should be approximately 3 mm apart.
(7) Take out the cultured cartilage and trim it as necessary using the shaped JACC template, etc. to fit the recipient site. Insert the cultured cartilage between the recipient site and the fixation patch with its flat surface on the bone side.

(8) Suture the fixation patch around the remaining half of perimeter to the surrounding cartilage. Separately, fix the fixation patch by the pull-out method.
(9) Ensure that there is no detachment of the fixation patch or leakage of the cultured cartilage when bending and stretching the knee. Close the wound according to the standard surgical procedure.

(No change)

Approval Conditions

1. The applicant is required to take necessary measures, such as disseminating the guidelines for proper use jointly prepared with relevant academic societies and offering seminars, to ensure that the product is used for eligible patients selected, by physicians and at medical institutions with adequate knowledge and experience in the treatment of knee osteoarthritis and a good understanding of the product's efficacy and safety.
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Attachment

Review Report (1)

January 21, 2025

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

Product Submitted for Approval

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2. Knee osteoarthritis

   Improvement of clinical symptoms of knee osteoarthritis by repairing hyaline cartilage-like tissue exclusively with a cartilage defect measuring 2 cm^2 or larger which do not respond to exercise therapy or other conservative treatments

(Underline denotes additions.)

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1. Transplantation planning
   (1) The marketing authorization holder sends the designated form to the treating physician upon request.
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(8) Suture the fixation patch around the remaining half of perimeter to the surrounding cartilage. Separately, fix the fixation patch by the pull-out method.
(9) Ensure that there is no detachment of the fixation patch or leakage of the cultured cartilage when bending and stretching the knee. Close the wound according to the standard surgical procedure.

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

JACC is an autologous cultured cartilage, which is prepared by culturing chondrocytes that have been isolated from patient's own cartilage tissue and embedded in atelocollagen gel. JACC was developed to fill and repair a full-thickness cartilage defect of the knee through the production of cartilage matrix, and thereby improve joint function. For transplantation of JACC, the JACC collagen patch or a periosteal patch, which has been harvested from the anteromedial surface of the proximal tibia, etc., is sutured and secured around the surrounding cartilage covering the recipient site to close the wound.

JACC was approved for the indications of traumatic cartilage defects and osteochondritis dissecans in July 2012.

1.2 Development history, etc.

Knee osteoarthritis (OA) is a condition associated with regressive changes, such as degeneration and wear of the cartilage tissue, osteophyte formation, knee joint deformity, and a decreased joint range of motion, resulting in pain during movements. Knee OA is classified as primary OA, which is caused by chronic mechanical irritation in addition to heredity or aging, or secondary OA, which occurs subsequent to trauma or meniscus removal, or in association with inflammatory or metabolic disorder. Patients with severe knee OA are likely to have difficulty in walking because of severe pain, leading to a significant decrease in quality of life (QOL) and activities of daily living (ADL).

Knee OA is conventionally treated by kinesitherapy, drug therapy with non-steroidal anti-inflammatory drugs (NSAIDs) or sodium hyaluronate (HA) products, or surgical therapies (radical dissection [debridement], high tibial osteotomy, and total knee replacement). None of these therapies provides curative treatment. In addition, there is no treatment to repair the defected cartilage of patients with knee OA. To address these challenges, JACC was developed with the expectation that JACC transplanted to a patient's cartilage defects would improve clinical symptoms of knee OA.

As part of the clinical development of JACC for the treatment of knee OA, a Japanese phase III study (Study J-TEC 002-3) was conducted in [redacted] 20[redacted] in patients who were diagnosed with knee OA and had localized cartilage defects. The results of Study J-TEC 002-3 served as the basis for this partial change application to add knee OA to the indications or performance of JACC.

JACC is approved only in Japan as of January 2025.

2. Quality and Outline of the Review Conducted by PMDA

The present application relates to a new indication, and no data related to quality were submitted.

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

Although the present application relates to a new indication, the data related to primary pharmacodynamics or performance had been evaluated during the review process for the initial approval of JACC, and thus, no new data have been submitted.

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

The present application relates to a new indication, and no data related to non-clinical safety were submitted.

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

The present application relates to a new indication, and no data related to biological disposition were submitted.

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

As, the applicant submitted the evaluation data on the efficacy and safety from 1 Japanese phase III study shown in Table 1.

Table 1. List of clinical study on efficacy and safety

Data category	Region	Study identifier	Phase	Study population	No. of subjects enrolled	Outline of dosage regimen	Main endpoints
Evaluation	Japan	J-TEC 002-3	III	Patients with knee OA	58	• JACC group: Transplantation of JACC • Control group: Intraarticular injections of 25 mg of purified HA into the knee joint, 5 consecutive doses per week	Efficacy Safety

6.1 Japanese phase III study (Study J-TEC 002-3) (Attachment 1, [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, open-label, parallel-group study was conducted in patients diagnosed with knee OA (target sample size, a total of 58 subjects [29 in the JACC group, 29 in the control group][1)]) at 15 study sites in Japan to verify the efficacy and safety of JACC in comparison with intraarticular injection with a HA product. Study J-TEC 002-3 consisted of a run-in period from informed consent up to immediately before the start of the JACC therapy in the JACC group and a treatment period from the start of the JACC or HA therapy up to 52 weeks after the start of either therapy, discontinuation of either therapy, or the end of follow-up of adverse events.

Table 2 shows inclusion and exclusion criteria.

1) The primary efficacy endpoint was the change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score at Week 52. Assuming expected values of -13.7 in the JACC group and -0.3 in the control group, and a standard deviation (SD) of 16.7, 26 subjects per group (52 in total) were needed to achieve a power of 80% with a two-sided significance level of 5%. Allowing for a dropout rate of 10%, the target sample size of 29 per group (58 in total) was determined.

Table 2. Inclusion and exclusion criteria

Inclusion criteria	1) Patients aged ≥20 years at the time of informed consent who are capable to give a written informed consent 2) Patients with a localized cartilage defect of ≥2 cm^2 3) Patients diagnosed with Grade 2 or 3 knee OA according to K-L rating scale[a)] as confirmed by X-ray 4) Patients with clinical symptom knee pain 5) Patients who have been on kinesitherapy or other conservative treatments for the last 3 months
Exclusion criteria	1) Patients who participated in previous clinical studies of ACC-01, or those who have received transplantation of JACC 2) Patients aged ≥75 years at the time of informed consent 3) Patients with BMI ≥30 4) Patients who have cartilage defects involving the entire knee joint, making fixation of a collagen patch or periosteal patch difficult 5) Patients with a severe knee varus or valgus deformity of ≥5° from the normal value (FTA 175°) 6) Patients who underwent any surgery including arthroscopy in the affected knee joint within the last 3 months 7) Patients who have concurrent meniscal injury requiring treatment in the affected knee joint, or underwent surgical treatment of the meniscal in the affected knee joint within the last 3 months 8) Patients with present or previous autoimmune disease, such as rheumatoid arthritis, psoriatic arthritis, gout or pseudogout, systemic lupus erythematosus, dermatomyositis, polymyositis, autoimmune thyroid disease, multiple arteritis, scleroderma, colitis ulcerative, Crohn's disease, Sjogren's syndrome, Reiter's syndrome, or mixed connective-tissue disease 9) Patients with a confirmed or suspected malignancy, or previous malignancy within the last 5 years 10) Patients who have a complication, etc. in the affected knee joint or anywhere in the body, making evaluation difficult as assessed by the investigator or subinvestigator 11) Patients with a history of hypersensitivity to antibiotics (gentamicin and amphotericin B) or aminoglycoside antibiotics 12) Patients with a history of hypersensitivity to animals (bovine and swine) 13) Patients with inadequately controlled diabetes 14) Patients with a history of anaphylactic reaction 15) Patients with a history of hypersensitivity to atelocollagen 16) Patients who are unable to undergo MRI scans 17) Patients who are participating in other clinical studies at the time of informed consent or planning to participate in other clinical studies while being on the study 18) Patients who are pregnant women or lactating women, or women who may possibly be pregnant or want to be pregnant while being on the study 19) Patients who are otherwise ineligible for participation in the study as assessed by the investigator or subinvestigator

a) The severity of joint deformity was rated using a 5-point scale from Grade 0 (none) to 4 in the ascending order of severity of the symptoms based on X-ray images.

The directions for use are as follows.

In the JACC group, JACC was manufactured for each subject using their own healthy cartilage tissue (approximately 0.4 g) that had been arthroscopically harvested from the subject's knee (non-weight-bearing site of the femoral medial or lateral condyle). For transplantation, the damaged cartilage was exposed, and then, the degenerative cartilage, etc. were removed to expose the subchondral bone, followed by transplantation of 1 JACC product to the defected area. The control group received intraarticular injections of an HA product approved in Japan (a dose of 25 mg of purified HA) into the knee joint, 5 consecutive doses every 1 week.

In order to avoid the effect on efficacy or safety evaluation of JACC, the following treatments were prohibited: Local anesthetics, corticosteroids, intraarticular injection of HA products, serotonin and norepinephrine reuptake inhibitors (SNRIs), or surgical treatment of the target knee joint.

Subjects received rehabilitation after the start of the JACC or HA therapy. The rehabilitation schedule in the JACC group was fixation to light flexion after transplantation to Day 7, non-weight-bearing

flexion/extension exercise from Day 8 to Day 21, partial weight-bearing flexion exercise from Day 22 to Day 35, and full weight-bearing flexion exercise after Day 36. The control group received rehabilitation appropriately (the same exercises as those for the JACC group) according to the subject's condition.

A total of 59 subjects provided informed consent. Of them, 58 subjects (27 in the JACC group, 31 in the control group) were assessed to be eligible for the study at screening, enrolled in the study, and randomized to either group. The safety analysis set for the run-in period consisted of 27 subjects in the JACC group who received an intradermal test. Of the subjects enrolled, 3 subjects (1 subject discontinued from the study before transplantation after tissue collection in the JACC group, 2 subjects discontinued from the study before the first dose in the control group) were excluded. The remaining 55 subjects (26 in the JACC group, 29 in the control group) received the JACC or HA therapy and were included in the safety analysis set for the treatment period. Of them, 54 subjects (26 in the JACC group, 28 in the control group) were included in the full analysis set (FAS), which was the primary efficacy analysis set. The remaining 1 subject (1 subject discontinued from the study after the first dose in the control group) was excluded. Table 3 shows the patient characteristics in the efficacy analysis set. Table 4 shows the details of transplantation of JACC.

Table 3. Subject characteristics (FAS)

			JACC	Control
Sample size			26	28
Sex		Male	13 (50.0)	14 (50.0)
		Female	13 (50.0)	14 (50.0)
Age (years)		Mean ± SD	48.7 ± 11.0	52.5 ± 9.3
		<65 years	24 (92.3)	25 (89.3)
		≥65 years	2 (7.7)	3 (10.7)
BMI (kg/m^2)		<25	9 (34.6)	11 (39.3)
		≥25	17 (65.4)	17 (60.7)
Affected site		Right knee	12 (46.2)	16 (57.1)
		Left knee	14 (53.8)	12 (42.9)
Duration		<1 year	10 (38.5)	10 (35.7)
		≥1 year	15 (57.7)	16 (57.1)
		Unknown	1 (3.8)	2 (7.1)
K-L classification		Grade 2	14 (53.8)	19 (67.9)
		Grade 3	12 (46.2)	9 (32.1)
MRI or arthroscopic information on cartilage defect	Number of cartilage defects	1	6 (23.1)	16 (57.1)
		2	15 (57.7)	8 (28.6)
		3	5 (19.2)	3 (10.7)
		4	0 (0.0)	1 (3.6)
	Cartilage defect site[a)]	Femoral medial condyle	16 (61.5)	22 (78.6)
		Femoral lateral condyle	7 (26.9)	7 (25.0)
		Femoral trochlea	14 (53.8)	3 (10.7)
		Patella	6 (23.1)	4 (14.3)
		Others	8 (30.8)	9 (32.1)
	Cartilage defect size (cm^2)[b)]	Mean ± SD	5.26 ± 2.28	5.45 ± 3.11
		<4	10 (38.5)	13 (46.4)
		≥4	16 (61.5)	15 (53.6)
Complication		None	3 (11.5)	2 (7.1)
		Yes	23 (88.5)	26 (92.9)
	Site	Affected joint	3 (13.0)	6 (23.1)
		Others	23 (100)	25 (96.2)
	Severity	Grade 1	14 (60.9)	21 (80.8)
		Grade 2	20 (87.0)	20 (76.9)
		Grade 3	0 (0.0)	2 (7.7)
		Grade 4	0 (0.0)	0 (0.0)
		Grade 5	0 (0.0)	0 (0.0)
Medical history		None	7 (26.9)	14 (50.0)
		Yes	19 (73.1)	14 (50.0)
	Site[c)]	Affected joint	17 (89.5)	11 (78.6)
		Others	5 (26.3)	4 (28.6)
Smoking history		Smoker	3 (11.5)	5 (17.9)
		Non smoker	18 (69.2)	13 (46.4)
		Previous smoker	5 (19.2)	10 (35.7)

Number of subjects (%)

a) All cartilage defects were counted for each subject.

b) Total area of all cartilage defects for each subject

c) Percentage (%) was calculated using the number of subjects with medical history as the parameter.

Table 4. Information on JACC transplantation

Sample size		26
Number of recipient sites	1	16 (61.5)
	2	8 (30.8)
	3	2 (7.7)
	4	0 (0.0)
Recipient site[a)]	Femoral medial condyle	15 (57.7)
	Femoral lateral condyle	7 (26.9)
	Femoral trochlea	12 (46.2)
	Patella	2 (7.7)
	Others	2 (7.7)
Area (cm^2)[b)]	Mean ± SD	6.33 ± 4.36
	<4	7 (26.9)
	≥4	19 (73.1)
Number of transplants	1	9 (34.6)
	2	12 (46.2)
	3	2 (7.7)
	4	3 (11.5)

Number of subjects (%)
a) All recipient sites were counted for each subject.
b) Total area of all recipient sites for each subject

The primary efficacy endpoint was the change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score at Week 52. Table 5 presents the results. The pre-treatment results were collected at screening visits from the completion of registration until the start of the JACC or HA therapy. The difference between the JACC and control groups was statistically significant, indicating the superiority of the JACC therapy to the control therapy.

Table 5. Change in WOMAC score at Week 52 (LOCF) (FAS)

Therapy group (number of subjects)		JACC (26)	Control (27)[a)]
Mean ± SD	Screening	30.49 ± 14.37	19.57 ± 9.89
	Week 52	10.10 ± 12.06	14.39 ± 13.46
	Change	-20.39 ± 10.09	-5.19 ± 10.85
Between-group difference in change [95% CI]		-15.21 [-20.99, -9.42]	
P value[a),b)]		<0.0001	

a) One subject in the control group had efficacy evaluation at the screening visit but was discontinued from the study at Week 6. The WOMAC data from this subject were excluded from the analysis because the subject took NSAIDs on the day of discontinuation. No imputation of the missing data by last observation carried forward (LOCF) was performed.
b) Student's t test

Safety results are presented below:
In the JACC group, adverse events were observed in 8 of 27 subjects (29.6%) after tissue harvest during the run-in period and 26 of 26 subjects (100%) during the treatment period. No serious adverse event, adverse event leading to discontinuation, or death occurred during any period.

In the control group, adverse events were observed in 12 of 29 subjects (41.4%) during the treatment period. No serious adverse event, adverse event leading to discontinuation, or death occurred.

6.R Outline of the review conducted by PMDA

6.R.1 Review policy

PMDA evaluated the efficacy and safety of JACC mainly based on the results of Study J-TEC 002-3 submitted as the evaluation data.

6.R.2 Efficacy

On the basis of the review results shown below, PMDA determined that JACC was shown to have a certain degree of efficacy in improving clinical symptoms of knee OA.

6.R.2.1 Design and efficacy endpoints of Study J-TEC 002-3

The applicant's explanation about the reasons for the open-label design of Study J-TEC 002-3:

- The JACC group required 2 surgeries, while the control group required intraarticular HA injections into the knee joint, 5 consecutive doses every 1 week. The pre-treatment, treatment methods, and the frequency of treatment differ between the JACC and control groups, which makes the use of a double-blind design difficult.
- The degree of invasiveness of treatment and the wound condition of the treated knee clearly differ between the 2 therapies, which makes the maintenance of blinding of the investigator challenging even with the use of a third-party evaluator.

The applicant's explanation about the appropriateness of defining the control therapy of Study J-TEC 002-3 as conservative treatment with intraarticular injections of a HA product:

- The standard treatment of Kellgren-Lawrence (K-L) Grade 2 or 3 knee OA, which was targeted by Study J-TEC 002-3, is conservative treatment with intraarticular HA injections or anti-inflammatory analgesics.
- HA products are similar to JACC in that the physical properties of HA protect the joint tissue to reduce pain, which is expected to improve clinical symptoms of knee OA.

The dosage regimen of the HA product was 5 consecutive injections every 1 week as determined according to its package insert.

The applicant's explanation about the appropriateness of the primary endpoint and follow-up period of Study J-TEC 002-3:

- WOMAC, which is an international patient-based scoring system commonly used to assess knee OA, is appropriate for efficacy evaluation in this study. Accordingly, the primary efficacy endpoint was the change from baseline in WOMAC score at Week 52.
- Study J-TEC 002, which was included in the application for the approved indications, demonstrated the efficacy and safety of JACC in patients with osteochondritis dissecans or traumatic cartilage defects during the 52-week follow-up. The study also suggested the safety and efficacy of JACC in 6 patients with knee OA. On the basis of these findings, subjects of Study J-TEC 002-3 were followed up for 52 weeks after the start of the treatment with the study product.

PMDA's view on the study design and primary endpoint:
It is understandable to conduct Study J-TEC 002-3 using an open-label design considering the differences in treatment procedures between the JACC group and the control group.

Study J-TEC 002-3 was conducted by defining the control therapy as conservative treatment with an HA product, which is commonly used to treat knee OA in clinical practice and protects the joint tissue to reduce pain. This control group using conservative treatment is acceptable.

The primary endpoint of Study J-TEC 002-3 was the change from baseline in WOMAC score. The therapeutic goals of knee OA are to reduce its symptoms such as pain and recover the joint function in order to improve ADL and QOL, thus the primary endpoint is acceptable. However, Study J-TEC 002-3 was an open-label study. Study staff's knowledge of subject allocation might have introduced bias in WOMAC scoring because it is a subjective index. Multidimensional evaluations including not only the results of the primary endpoint but also those of the secondary endpoints, including the objective endpoints, are required.

6.R.2.2 Efficacy results

The applicant's explanation about the efficacy results of Study J-TEC 002-3:

As shown in Table 5, the between-group difference [95% confidence interval (CI)] in the change in WOMAC score at Week 52, the primary efficacy endpoint, was -15.21 [-20.99, -9.42] in the efficacy analysis set. The difference between the JACC and control groups was statistically significant, indicating the superiority of the JACC therapy to the control therapy. There was an imbalance in the screening WOMAC score between the groups (Table 5). The between-group difference [95% CI] in the change in WOMAC score at Week 52 estimated using a multiple regression model with the screening WOMAC score and each group as covariates was -11.69 [-17.63, -5.75]. The difference was statistically significant as in the primary analysis ($P = 0.0002$, Wald test).

Concomitant medications and therapies that might affect the evaluation of the primary endpoint were addressed and discussed as follows:

- Corticosteroids were used in 5 subjects (all in the JACC group) either intravenously or orally. The shortest interval between the end of steroid use and WOMAC score assessment was 27 days. On the basis of their biological half-lives, these concomitant medications are unlikely to have affected the efficacy evaluation.
- SNRI was used in 1 subject (control group). The interval between the end of steroid use and WOMAC score assessment was 42 days. This concomitant medication is unlikely to have affected the efficacy evaluation.
- Arthrocentesis was performed in 13 subjects (9 in the JACC group, 4 in the control group). The shortest interval between the arthrocentesis and WOMAC score assessment was 12 days. Since the effect of arthrocentesis on clinical symptoms lasts for approximately 1 week (*Knee Surg Sports Traumatol Arthrosc.* 2014;22:226-32), this concomitant therapy is unlikely to have affected the efficacy evaluation.
- For rehabilitation after the start of either therapy, a rehabilitation procedure manual was prepared to ensure that both the JACC and control groups could receive the same rehabilitation as much as possible, except for programs specific to perioperative or operative procedures. The details of rehabilitation were recorded for each subject. No deviation from the prescriptions was identified in any subjects.

The above analysis indicates that the effects of these concomitant medications and therapies on the results of the primary endpoint were minimized.

The following secondary endpoints were used in the study:

1) Changes in the scores of WOMAC subscales (pain, stiffness, and physical function) at Week 52

The change from baseline in the score of each WOMAC subscale[2)] at post-treatment visit tended to improve in the JACC group compared with the control group for all the subscales (Table 6).

Table 6. Changes in the scores of WOMAC subscales (pain, stiffness, and physical function) at Week 52 (LOCF) (FAS)

Subscale	Therapy group (number of subjects)	Mean ± SD			Between-group difference in change [95% CI]
		Screening	Week 52	Change	
Pain	JACC (26)	6.4 ± 3.0	2.0 ± 2.7	-4.5 ± 2.8	-3.0
	Control (27)[a)]	5.2 ± 2.6	3.7 ± 3.4	-1.4 ± 3.4	[-4.7, -1.3]
Stiffness	JACC (26)	3.0 ± 1.6	1.2 ± 1.4	-1.8 ± 1.4	-1.2
	Control (27)[a)]	2.1 ± 1.4	1.5 ± 1.4	-0.6 ± 1.4	[-1.9, -0.4]
Physical function	JACC (26)	19.9 ± 10.5	6.6 ± 8.1	-13.3 ± 6.8	-10.4
	Control (27)[a)]	11.5 ± 7.8	8.6 ± 9.3	-2.9 ± 7.8	[-14.4, -6.4]

a) One subject in the control group had efficacy evaluation at the screening visit but was discontinued from the study at Week 6. The WOMAC data from this subject were excluded from the analysis because the subject took NSAIDs on the day of discontinuation. No imputation of the missing data by LOCF was performed.

2) Change in Lysholm Knee Score (LKS) at Week 52

LKS, which is the investigator-initiated assessment, tended to improve in the JACC group compared with the control group (Table 7).

Table 7. Change in LKS at Week 52 (LOCF) (FAS)

Therapy group (number of subjects)	Mean ± SD			Between-group difference in change [95% CI]
	Screening	Week 52	Change	
JACC (26)	59.8 ± 14.9	87.4 ± 14.1	27.6 ± 19.8	17.9
Control (27)[a)]	63.8 ± 13.7	73.4 ± 18.0	9.6 ± 20.1	[7.0, 28.9]

a) One subject in the control group had efficacy evaluation at the screening visit but was discontinued from the study at Week 6. The LKS data from this subject were excluded from the analysis because the subject took NSAIDs on the day of discontinuation. No imputation of the missing data by LOCF was performed.

3) Magnetic resonance imaging (MRI)_T2 value assessment

The T2 ratio between the surrounding healthy site and the repaired site at Week 52 was analyzed in order to assess whether hyaline cartilage-like tissue similar to the surrounding healthy site was formed. The JACC group had T2 ratios that decreased to approximately 1 at all recipient sites, showing a tendency of remarkable improvement, while the control group tended to show slight improvement (Table 8).

Table 8. MRI_T2 value assessment at Week 52 (FAS)

Therapy group		Screening	Week 52 (missing data not imputed)[a)]	Week 52 (missing data imputed)[b)]
JACC	Number of recipient sites	38	37	38
	Mean ratio (SD)	2.719 (±2.227)	1.390 (±0.814)	1.386 (±0.803)
Control	Number of cartilage defect sites	43[c)]	28	43
	Mean ratio (SD)	2.985 (±3.252)	2.159 (±1.131)	2.620 (±2.207)

a) One subject (1 recipient site) in the JACC group and 10 subjects (15 cartilage defect sites) in the control group had no evaluation at Week 52.

b) When data at Week 52 or the day of discontinuation are missing, the screening data were used as the final evaluation data.

c) One subject (2 cartilage defect sites) in the control group had no evaluation.

2) Higher scores indicate severer symptoms. Each subscale is scored from 0 to 4 points. The pain subscale consists of 5 que7stions with a total score up to 20 points. The physical function subscale consists of 17 questions with a total score up to 68 points. The stiffness subscale consists of 2 questions with a total score up to 8 points.

4) 3D magnetic resonance observation of cartilage repair tissue (MOCART) score (MRI assessment) at Week 52

The 3D MOCART score (*Invest Radiol*. 2009;44:603-12) at Week 52 was analyzed in order to qualitatively assess the condition of all layers of the repaired sites in comparison with the surrounding healthy cartilage. Defect fill, cartilage interface, bone interface, surface, signal intensity, subchondral lamina, and subchondral bone scores tended to improve, with tissue similar to that of the healthy cartilage, at Week 52 in the JACC group compared with the control group. Structure, chondral osteophytes, bone marrow edema, and effusion scores showed no clear difference between the groups (Table 9). The analysis including the subject who discontinued from the study demonstrated a similar tendency.

Table 9. 3D MOCART score (MRI assessment) at Week 52 (FAS)

Parameter		Week 52 (missing data not imputed by LOCF)[a)]		Week 52 (missing data imputed by LOCF)[b),c)]	
		JACC	Control	JACC	Control
Number of transplantation/cartilage defect sites		37	28	38	43
Defect fill	0%	1 (2.7)	6 (21.4)	1 (2.6)	9 (20.9)
	0%-25%	3 (8.1)	13 (46.4)	3 (7.9)	20 (46.5)
	25%-50%	3 (8.1)	6 (21.4)	3 (7.9)	10 (23.3)
	50%-75%	2 (5.4)	3 (10.7)	2 (5.3)	4 (9.3)
	75%-100%	19 (51.4)	0 (0.0)	20 (52.6)	0 (0.0)
	100%	6 (16.2)	0 (0.0)	6 (15.8)	0 (0.0)
	100%-125%	2 (5.4)	0 (0.0)	2 (5.3)	0 (0.0)
	125%-150%	1 (2.7)	0 (0.0)	1 (2.6)	0 (0.0)
	150%-200%	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	>200%	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cartilage interface (Sagittal)	Complete	6 (16.2)	0 (0.0)	6 (15.8)	1 (2.3)
	Demarcating border visible (split-like)	23 (62.2)	3 (10.7)	24 (63.2)	6 (14.0)
	Defect visible <50%	5 (13.5)	4 (14.3)	5 (13.2)	6 (14.0)
	Defect visible >50%	3 (8.1)	21 (75.0)	3 (7.9)	30 (69.8)
Cartilage interface (Coronal/Axial)	Complete	6 (16.2)	0 (0.0)	6 (15.8)	1 (2.3)
	Demarcating border visible (split-like)	23 (62.2)	3 (10.7)	24 (63.2)	6 (14.0)
	Defect visible <50%	5 (13.5)	4 (14.3)	5 (13.2)	6 (14.0)
	Defect visible >50%	3 (8.1)	21 (75.0)	3 (7.9)	30 (69.8)
Bone interface	Complete	34 (91.9)	17 (60.7)	35 (92.1)	30 (69.8)
	Partial delamination	2 (5.4)	1 (3.6)	2 (5.3)	3 (7.0)
	Complete delamination	1 (2.7)	10 (35.7)	1 (2.6)	10 (23.3)
	Delamination of periosteal flap	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Surface	Surface intact	12 (32.4)	0 (0.0)	12 (31.6)	1 (2.3)
	Surface damaged <50% of depth	20 (54.1)	3 (10.7)	21 (53.3)	4 (9.3)
	Surface damaged >50% of depth	5 (13.5)	25 (89.3)	5 (13.2)	38 (88.4)
	Adhesions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Structure	Homogeneous	6 (16.2)	2 (7.1)	6 (15.8)	2 (4.7)
	Inhomogeneous or cleft formation	31 (83.8)	26 (92.9)	32 (84.2)	41 (95.3)
Signal intensity	Normal	1 (2.7)	0 (0.0)	1 (2.6)	0 (0.0)
	Nearly normal	31 (83.8)	11 (39.3)	31 (84.2)	12 (27.9)
	Abnormal	5 (13.5)	17 (60.7)	5 (13.2)	31 (72.1)
Subchondral lamina	Intact	18 (48.6)	6 (21.4)	19 (50.0)	16 (37.2)
	Not intact	19 (51.4)	22 (78.6)	19 (50.0)	27 (62.8)
Chondral Osteophytes	Absent	36 (97.3)	26 (92.9)	37 (97.4)	37 (86.0)
	Osteophytes <50% of the thickness of the cartilage transplant	1 (2.7)	1 (3.6)	1 (2.6)	4 (9.3)
	Osteophytes >50% of the thickness of the cartilage	0 (0.0)	1 (3.6)	0 (0.0)	2 (4.7)
Bone marrow edema	Absent	24 (64.9)	12 (42.9)	25 (65.8)	22 (51.2)
	Small (<1 cm)	8 (21.6)	12 (42.9)	8 (21.1)	14 (32.6)
	Medium (<2 cm)	5 (13.5)	4 (14.3)	5 (13.2)	7 (16.3)
	Large (<4 cm)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Diffuse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subchondral bone	Intact	22 (59.5)	11 (39.3)	23 (60.5)	20 (46.5)
	Granulation tissue	11 (29.7)	5 (17.9)	11 (28.9)	7 (16.3)
	Cyst	4 (10.8)	2 (7.1)	4 (10.5)	2 (4.7)
	Sclerosis	0 (0.0)	10 (35.7)	0 (0.0)	14 (32.6)
Effusion	Absent	20 (54.1)	11 (39.3)	21 (55.3)	15 (34.9)
	Small	15 (40.5)	12 (42.9)	15 (39.5)	20 (46.5)
	Medium	2 (5.4)	5 (17.9)	2 (5.3)	7 (16.3)
	Large	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)

Number of subjects (%)

a) One subject (1 recipient site) in the JACC group and 10 subjects (15 cartilage defect sites) in the control group had no evaluation at Week 52.

b) One subject (2 cartilage defect sites) in the control group had no evaluation.

c) Missing data in the subject discontinued from the study were imputed by the data on the day of discontinuation. When data at Week 52 or the day of discontinuation are missing, the final evaluation data were recorded as missing.

5) International Cartilage Repair Society (ICRS) score (arthroscopic assessment)

For direct observation and assessment of the condition of the knee joint, invasive arthroscopy was performed in subjects who consented to this assessment separately from the consent to the study. The

ICRS score[3)] was determined from arthroscopic data for 23 recipient sites in 16 subjects in the JACC group and 1 cartilage defect site in 1 subject in the control group at Week 52 or the day of discontinuation.

The mean ICRS scores (standard deviation [SD]) in the JACC group were 3.4 (±0.8) for the degree of defect repair, 2.8 (±1.1) for the border zone, and 3.0 (±0.9) for macroscopic appearance. The mean ICRS scores in the control group were 1 (-) for macroscopic appearance and 0 for the other parameters (Table 10). Note that these results were from 1 subject.

Table 10. ICRS score (arthroscopic assessment) at Week 52 (FAS)

	Therapy group	Number of transplantation/cartilage defect sites	Mean (SD)
Degree of defect repair	JACC	23	3.4 (±0.8)
	Control	1	0 (-)
Border zone	JACC	23	2.8 (±1.1)
	Control	1	0 (-)
Macroscopic appearance	JACC	23	3.0 (±0.9)
	Control	1	1 (-)
Total	JACC	23	9.1 (±2.5)
	Control	1	1 (-)

6) Histology

Histological assessment was performed at Week 52 in 12 subjects in the JACC group who consented to biopsy. Recipient sites were 18 in total from 12 subjects. The results of fast green + Safranin-O staining and Type II collagen immunostaining were positive for all of the 6 femoral medial condyles tested. Femoral lateral condyles were tested at 4 sites. The results were positive at 3 sites and negative at 1 site. Femoral trochleae were tested at 6 sites, of which 5 were positive and 1 was negative. Tibial lateral condyles were tested at 2 sites, and both were positive.

7) Number of days on NSAIDs

The weekly mean number of days on NSAIDs (SD) during the allowance period (35-49 days for Week 6, 70-98 days for Week 12, 147-189 days for Week 24, and 336-392 days for Week 52), excluding the prohibited concomitant medication period (1 week prior to WOMAC assessment), was calculated and evaluated for each post-treatment period based on the patient's diary data. No pre-treatment data were collected regarding the number of days on NSAIDs. A period, during which data were missing due to a lack of entries in the patient's diary or study discontinuation, was excluded from the calculation.

The weekly mean number of days on NSAIDs (SD) for each period in the JACC group was 2.22 (±3.08) at Week 6, 2.63 (±2.93) at Week 12, 1.73 (±2.56) at Week 24, and 0.31 (±0.85) at Week 52. This parameter increased up to Week 12 and decreased after Week 24. The parameter in the control group was 0.89 (±2.32) at Week 6, 0.91 (±2.11) at Week 12, 0.90 (±1.97) at Week 24, and 0.65 (±1.54) at Week 52, showing little change over time regardless of period (Table 11).

[3)] This scoring system assesses the condition of the knee joint using the degree of cartilage repair determined by arthroscopic observation (ICRS). For this examination, an arthroscopy is inserted into the knee joint through a skin incision made under anesthesia. The scoring system consists of the degree of defect repair, border zone, and macroscopic appearance. Each parameter is scored from 0 to 4 points. Higher scores indicate better knee joint conditions.

Table 11. Number of post-treatment days on NSAIDs (FAS)

Therapy group	Assessment period[a)]	Week 6	Week 12	Week 24	Week 52
JACC	Number of subjects[b)]	18	26	26	14
	Mean (SD)	2.22 (±3.08)	2.63 (±2.93)	1.73 (±2.56)	0.31 (±0.85)
	Median (Min, Max)	0.0 (0.0, 7.0)	1.60 (0.0, 7.0)	0.25 (0.0, 7.0)	0.0 (0.0, 3.0)
Control	Number of subjects[b)]	9	23	21	13
	Mean (SD)	0.89 (±2.32)	0.91 (±2.11)	0.90 (±1.97)	0.65 (±1.54)
	Median (Min, Max)	0.0 (0.0, 7.0)	0.0 (0.0, 7.0)	0.0 (0.0, 7.0)	0.0 (0.0, 4.5)

a) Allowance period for each assessment period, except for 1 week prior to WOMAC assessment
b) Number of subjects on NSAIDs

8) Repair by hyaline cartilage-like tissue

Repair by hyaline cartilage-like tissue was assessed in a comprehensive manner by the data monitoring committee,[4)] independent of the study site and the sponsor, in 26 subjects in the JACC group and 27 subjects, excluding 1 subject with missing data (2 cartilage defect sites), in the control group based on MRI, ICRS (arthroscopy), and histological data at Week 52.

The JACC group had 38 recipient sites. Repair by hyaline cartilage-like tissue was observed at 37 of 38 sites (97.4%) in 25 subjects. No repair by hyaline cartilage-like tissue was observed at 1 of 38 sites (2.6%) in 1 subject. The control group had 43 cartilage defect sites. No repair by hyaline cartilage-like tissue was observed at any of the sites.

In summary, the changes in investigator-assessed LKS and patient-based WOMAC score showed a similar tendency, indicating that the change in WOMAC score used as the primary endpoint was appropriately assessed. Repair by hyaline cartilage-like tissue was confirmed by the data monitoring committee. The applicant determined that the study demonstrated the efficacy of JACC.

PMDA's view:

Although there was an imbalance in the results of WOMAC score, WOMAC subscale scores, and LKS at screening between the groups in Study J-TEC 002-3, the change from baseline in WOMAC score at Week 52, the primary analysis of the primary endpoint, showed a statistically significant difference (Table 5). The analysis using a multiple regression model with the screening WOMAC score and each therapy group as covariates demonstrated a statistically significant difference as in the primary analysis. The changes from baseline in WOMAC subscale scores and LKS at Week 52, the secondary endpoints, (Tables 6 and 7) also indicated improvement of clinical symptoms in the JACC group compared with the control group. In addition, MRI_T2, MRI, arthroscopic, and histological findings suggested improvement. JACC was shown to have a certain degree of efficacy in improving clinical symptoms of knee OA.

Considering that Study J-TEC 002-3 provides data only up to Week 52, information regarding the long-term efficacy of JACC in patients with knee OA beyond Week 53 should be collected in the post-marketing setting.

4) The data monitoring committee was installed in order to assess MRI_T2 values, repair by hyaline cartilage-like tissue, etc. among the efficacy endpoints, independently of the study site and the sponsor. Prior to assessments by the data monitoring committee, the subject's identification information such as the subject's number was masked. The results of blind assessments were presented to the investigator and subinvestigator.

6.R.3 Safety

PMDA's view:

On the basis of the discussion shown below, the risk associated with transplantation of JACC is acceptable provided that information regarding adverse events, etc. reported in Study J-TEC 002-3 is provided appropriately to healthcare professionals using materials, etc. and that physicians with adequate knowledge and experience in treatment of knee OA take appropriate measures such as monitoring and management of adverse events based on the information provided.

6.R.3.1 Incidences of adverse events in Study J-TEC 002-3

The applicant's explanation about the safety of JACC:

Table 12 presents adverse events that occurred during the run-in and treatment periods in the JACC group, and those during the treatment period in the control group in Study J-TEC 002-3. Neither serious adverse events nor deaths occurred.

A Grade ≥3 adverse event of application site pain occurred during the treatment period in 1 of 26 subjects (3.8%) in the JACC group, for which a causal relationship to the JACC therapy could not be ruled out.

Table 12. Major adverse events observed in Study J-TEC 002-3 (safety analysis set)

	JACC		Control
	Run-in period[a)] N = 27	Treatment period N = 26	Treatment period N = 29
All adverse events	8 (29.6)	26 (100)	12 (41.4)
Serious adverse events	0	0	0
Grade ≥3 adverse events	0	1 (3.8)	1 (3.4)
Adverse events reported by ≥5% of subjects during the run-in period[a)] in the JACC group, during the treatment period in the JACC group, or during the treatment period in the control group			
Application site pain	0	20 (76.9)	0
Procedural pain	7 (25.9)	0	0
Pyrexia	0	5 (19.2)	0
Application site swelling	0	5 (19.2)	0
Venous thrombosis limb	0	5 (19.2)	0
Arthralgia	1 (3.7)	4 (15.4)	1 (3.4)
Joint effusion	1 (3.7)	2 (7.7)	1 (3.4)
Pruritus	0	2 (7.7)	0
Arthrofibrosis	0	2 (7.7)	0
Joint swelling	0	2 (7.7)	0
Nasopharyngitis	0	1 (3.8)	2 (6.9)
Injection site pain	0	0	2 (6.9)
Ligament sprain	0	0	2 (6.9)

Number of subjects with events (incidence %)
Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) Ver26.1
a) From the end of tissue harvest to immediately before transplantation of JACC during the run-in period

The applicant's explanation about the adverse events reported in Study J-TEC 002-3:

In the JACC group, adverse events occurred in 8 of 27 subjects (29.6%) after tissue harvest during the run-in period. Adverse events for which a causal relationship to the JACC therapy could not be ruled out occurred in 7 of 27 subjects (25.9%). All of these were classified as procedural pain, for which a causal relationship to the tissue harvest procedure could not be ruled out.

In the JACC group, adverse events occurred in 26 of 26 subjects (100%) during the treatment period. Adverse events for which a causal relationship to the JACC therapy could not be ruled out occurred in

24 of 26 subjects (92.3%, 39 events); i.e., tissue harvest procedure-related events in 1 of 26 subjects (3.8%), transplantation procedure-related events in 24 of 26 subjects (92.3%), and JACC-related events in 3 of 26 subjects (11.5%). The adverse event for which a causal relationship to the tissue harvest procedure could not be ruled out was arthrofibrosis in 1 of 26 subjects (3.8%). Adverse events for which a causal relationship to the transplantation procedure could not be ruled out included application site pain in 20 of 26 subjects (76.9%), application site swelling in 5 of 26 subjects (19.2%), pyrexia in 3 of 26 subjects (11.5%), arthrofibrosis in 2 of 26 subjects (7.7%), and blister, dermatitis contact, bone cyst, bursitis, myalgia, application site cyst, and C-reactive protein increased, each in 1 of 26 subjects (3.8%). Adverse events for which a causal relationship to JACC could not be ruled out included application site pain in 2 of 26 subjects (7.7%), and C-reactive protein increased and graft delamination, each in 1 of 26 subjects (3.8%).

In the control group, adverse events occurred in 12 of 29 subjects (41.4%) during the treatment period. An adverse event for which a causal relationship to the control therapy could not be ruled out occurred in 1 of 29 subjects (3.4%). The event was injection site pain, for which a causal relationship to the procedure could not be ruled out.

Neither allergic symptoms nor unknown infections for which a causal relationship to the JACC therapy could not be ruled out occurred after transplantation of JACC. All subjects had JACC successfully manufactured from their harvested source tissue.

All adverse events reported in Study J-TEC 002-3 were analyzed by time to onset. The following adverse events for which a causal relationship to either therapy could not be ruled out occurred between the start of the therapy and Week 6: Application site pain in 20 of 26 subjects (76.9%), application site swelling in 5 of 26 subjects (19.2%), pyrexia in 3 of 26 subjects (11.5%), and blister, dermatitis contact, bursitis, myalgia, and C-reactive protein increased, each in 1 of 26 subjects (3.8%) in the JACC group; and injection site pain in 1 of 29 subjects (3.4%) in the control group. No adverse event for which a causal relationship to either therapy could not be ruled out occurred between Weeks 7 and 12. The only adverse event for which a causal relationship to either therapy could not be ruled out occurring between Weeks 12 and 24 was bone cyst in 1 of 26 subjects (3.8%) in the JACC group. Adverse events for which a causal relationship to either therapy could not be ruled out occurring after Week 25 were fibrous adhesion in 2 of 26 subjects (7.7%), and application site cyst and graft delamination, each in 1 of 26 subjects (3.8%) in the JACC group. No event occurred in the control group after Week 25.

In summary, no problematic adverse event occurred in Study J-TEC 002-3.

PMDA discussed the safety of JACC with a focus on graft delamination, application site pain, and venous thrombosis limb, as shown below.

6.R.3.2 Safety based on each event

6.R.3.2.1 Graft delamination

The applicant's explanation about graft delamination after transplantation of JACC:
In Study J-TEC 002-3, graft delamination occurred in 1 of 26 subjects (3.8%). The subject was a 42-years old man. The event occurred at Week 50 and did not resolve. The event might have resulted from multiple causes such as hypertrophy and load-bearing at the recipient site. No clinical symptom associated with graft delamination was reported. No additional intervention was required.

An autologous periosteal patch isolated from the patient has been used as a fixation patch in transplantation of JACC since its approval for the existing indications or performance in 2012. In 2019, a collagen patch was added to the secondary components of JACC (partial change approval as of January 31, 2019). The collagen patch was also used in this study. In order to examine the effect of the collagen patch on safety, the incidence of graft delamination, occurring Week 53 onward as an adverse event for which a causal relationship to JACC or the transplant procedure could not be ruled out, in the treatment for the approved indications or performance, was analyzed by time to onset and fixation patch type based on the information collected in the use-results survey for the approved indications or performance. The fixation patches included in this analysis were the collagen patch in 108 subjects, periosteal patch in 645 subjects, and unknown in 2 subjects. In the collagen patch subgroup, graft delamination for which a causal relationship to JACC or the transplantation procedure could not be ruled out occurred in 3 of 108 subjects (2.8%) up to Week 52 and 2 of 108 subjects (1.9%) from Week 53 onward. In the periosteal patch subgroup, graft delamination for which a causal relationship to JACC or the transplantation procedure could not be ruled out occurred in 26 of 645 subjects (4.0%) up to Week 52 and 44 of 645 subjects (6.8%) from Week 53 onward. No graft delamination for which a causal relationship to JACC or the transplantation procedure could not be ruled out occurred in 2 subjects who used an unknown fixation patch. These findings suggest that the use of the collagen patch for fixation reduces the risk of graft delamination.

Since the clinical studies provide only limited information, information regarding graft delamination is planned to be collected as a significant adverse event in the use-results survey in the post-marketing setting.

PMDA's view:
In Study J-TEC 002-3, graft delamination was reported as an adverse event for which a causal relationship to JACC could not be ruled out. This event also occurred from Week 53 onward in the use-results survey for the approved indications or performance. Graft delamination should be an adverse event requiring special attention associated with the JACC therapy. Information regarding the event should continue to be collected in the post-marketing setting.

6.R.3.2.2 Application site pain

The applicant's explanation about application site pain after transplantation of JACC:
In Study J-TEC 002-3, application site pain occurred in 20 of 26 subjects (76.9%) in the JACC group during the treatment period. A causal relationship to JACC could not be ruled out for all events in the 20 subjects, including transplantation procedure-related event in 20 of 26 subjects (76.9%) and JACC-

related event in 2 of 26 subjects (7.7%). The severity of the event was Grade 1 in 1 of 26 subjects (3.8%), Grade 2 in 18 of 26 subjects (69.2%), and Grade 3 in 1 of 26 subjects (3.8%). All of the 20 subjects experienced the event within 2 days post-transplant. For intervention, 19 subjects received analgesics and 1 subject underwent arthrocentesis. The outcomes of the event were recovery or recovering in 10 days after onset in 12 subjects, recovery in 11 to 30 days after onset in 5 subjects, recovery at 90 days post-transplant in 1 subject, recovery at 282 days post-transplant in 1 subject, and non-recovery in 1 subject. All cases were not serious.

Since transplantation of JACC involves surgeries, pain associated with invasive surgeries cannot be avoided. Considering the seriousness, etc. of the event, its risk range is acceptable.

PMDA's view:
Since application site pain that occurred after transplantation of JACC was not severe and recovered within a short period of time in almost all of the subjects, the risk of pain associated with transplantation of JACC is acceptable. Relevant information should continue to be provided to healthcare professionals using a manual or other materials so that they can manage pain as necessary.

6.R.3.2.3 Venous thrombosis limb

The applicant's explanation about venous thrombosis limb after transplantation of JACC:
In Study J-TEC 002-3, venous thrombosis limb occurred in 5 of 26 subjects (19.2%). Thrombosis developed in the lower thigh on the transplantation side of JACC in all of the 5 subjects. The time from transplantation to onset was 8 days in 4 subjects and 9 days in 1 subject. No event was associated with any clinical symptom. Postoperative echography performed according to the institutional protocol revealed findings suggesting thrombosis. All subjects received oral anticoagulants. The outcomes of the event were recovery and recovering. All of the cases were caused by non-weight bearing. No pulmonary embolism was reported.

The risk of thrombosis associated with the JACC therapy is expected to be similar to the risk associated with knee arthroscopic surgery because the level of surgical invasion is similar in these surgical procedures. For arthroscopic anterior cruciate ligament reconstruction, a knee arthroscopic surgery, the incidence of deep vein thrombosis (DVT) was 21.2% (The Japanese Orthopaedic Association. Guidelines for the prevention of symptomatic venous thromboembolism 2017 [in Japanese]. 2017:51-3). In comparison with this figure, the incidence of thrombosis in this study is not especially high. In addition, postoperative thrombosis in Study J-TEC 002-3 was mild in severity and transient in all subjects. Its risk is acceptable.

PMDA's view:
The risk of thrombosis associated with the JACC therapy is acceptable based on the incidence and seriousness of venous thrombosis limb that occurred after transplantation of JACC in the study in comparison with those associated with other lower limb surgeries. Nevertheless, prophylaxis of thrombosis after lower limb surgery is essential. It is useful to continue to provide relevant information to healthcare professionals using materials.

6.R.3.3 Long-term safety

The applicant's explanation about long-term safety after transplantation of JACC:
Study J-TEC 002-3 evaluated the efficacy and safety of the JACC therapy up to Week 52 according to the protocol. No follow-up efficacy or safety data are available from Week 53 onward.

In order to investigate the possible increased risk of adverse events from Week 53 onward, adverse events that occurred at Week 53 or later were analyzed based on post-marketing information from patients who received the JACC therapy for the approved indications or performance. Table 13 presents the incidences of adverse events occurring at Week 53 or later.

Table 13. Adverse events occurring at Week 53 or later in the approved indications or performance

Number of subjects	755
All adverse events	112 (14.8)
Adverse events reported by ≥1% of patients	
Graft delamination	54 (7.2)
Joint effusion	24 (3.2)
Graft complication	21 (2.8)
Cartilage injury	8 (1.1)

Number of subjects with events (incidence %)
MedDRA/J Ver27.0

Among the adverse events involving knee joints observed after JACC therapy for the approved indications or performance, "graft delamination" was only the event occurring at a ≥1% higher incidence from Week 53 onward than the incidence up to Week 52 for which a causal relationship to JACC or the surgical procedure could not be ruled out. Knee OA shows similar characteristics of defects to those in traumatic cartilage defects or osteochondritis dissecans, the approved indications, despite its different etiology. Thus, JACC therapy is considered to follow a similar healing process and will not show significantly different safety profile.

PMDA's view:
To ensure the long-term safety after transplantation of JACC, attention should be paid to the onset of graft delamination because this adverse event occurred at Week 53 or later in patients who received the JACC therapy for the approved indications or performance. However, no long-term safety data of JACC for knee OA are available from the study. As for the approved indications or performance, relevant data should be collected appropriately for 2 years after JACC transplantation in the post-marketing setting, and healthcare professionals should be cautioned about any newly identified problematic events promptly.

6.R.4 Indications or performance

The proposed indications or performance and the proposed precautions concerning indications or performance are shown below:

Indications or Performance (Underline denotes additions.)

1. Traumatic cartilage defects or osteochondritis dissecans

   Alleviation of clinical symptoms of traumatic cartilage defects or osteochondritis dissecans of the knee exclusively with a cartilage defect measuring 4 cm^2 or larger for which there are no other treatment options

2. Knee osteoarthritis

   Improvement of clinical symptoms of knee osteoarthritis by repairing hyaline cartilage-like tissue exclusively with a cartilage defect measuring 2 cm^2 or larger which do not respond to exercise therapy or other conservative treatments

Precautions Concerning Indications or Performance

(1) JACC should not be indicated for patients who are eligible for standard surgical therapies. JACC is a therapeutic option when no other therapy is available.

(2) The possibility of treating the patient without using JACC should be adequately explored. The use of JACC should be carefully considered based on full understanding of the descriptions in the Clinical Studies section, etc. and the efficacy and safety of JACC.

(3) No data are available showing the engraftment of the transplanted cultured cartilage and subsequent formation of cartilage tissue.

(4) JACC should be indicated for patients with a defect site that retains arthroscopically confirmed surrounding cartilage to allow for the suture of a fixation patch.

For the following reasons, PMDA asked the applicant to reconsider the proposed indications or performance and the proposed precautions concerning indications or performance based on the discussion in Sections "6.R.2 Efficacy" and "6.R.3 Safety."

- Whether the changes observed in clinical symptoms occurred as a result of repairing hyaline cartilage-like tissue remains unproven.
- The availability of the cartilage around defects to which a fixation patch can be sutured is not an eligibility criterion specific to knee OA.
- Patients eligible for the JACC therapy should be the patient population of Study J-TEC 002-3 in whom the efficacy and safety of this therapy were confirmed. Eligibility criteria regarding K-L grades and alignment should be defined appropriately.

The applicant reconsidered the indications or performance and the proposed precautions concerning indications or performance, and proposed the following modifications.

Indications or Performance (Underline denotes additions. Strikethrough denotes deletions.)

1. Traumatic cartilage defects or osteochondritis dissecans

   Alleviation of clinical symptoms of traumatic cartilage defects or osteochondritis dissecans of the knee exclusively with a cartilage defect measuring 4 cm^2 or larger for which there are no other treatment options

2. Knee osteoarthritis

Improvement of clinical symptoms of knee osteoarthritis ~~by repairing hyaline cartilage-like tissue,~~ exclusively with a cartilage defect measuring 2 cm^2 or larger which do not respond to exercise therapy or other conservative therapies~~treatment~~

Precautions Concerning Indications or Performance (Underline denotes changes.)

1. Traumatic cartilage defects or osteochondritis dissecans
   (1) JACC should not be indicated for patients who are eligible for standard surgical therapies. JACC is a therapeutic option when no other therapy is available.
   (2) The possibility of treating the patient without using JACC should be adequately explored. The use of JACC should be carefully considered based on full understanding of the descriptions in the Clinical Studies section, etc. and the efficacy and safety of JACC.
   (3) No data are available showing the engraftment of the transplanted cultured cartilage and subsequent formation of cartilage tissue.
   (4) JACC should be indicated for patients with a defect site that retains arthroscopically confirmed surrounding cartilage to allow for the suture of a fixation patch.

2. Knee osteoarthritis
   (1) The use of JACC should be carefully considered with full understanding of the information in the Clinical Studies section, etc. and the efficacy and safety of JACC.
   (2) The use of JACC should be carefully considered for patients with knee osteoarthritis whose clinical symptoms persist even after conservative therapies (e.g., kinesitherapy and drug therapy).
   (3) JACC should be indicated for patients with a defect site that retains arthroscopically confirmed surrounding cartilage to allow for the suture of a fixation patch.
   (4) Eligible patients for the JACC therapy should be selected with reference to the study population (patients who have Kellgren-Lawrence Grade 2 or 3 knee OA and a knee varus or valgus deformity of <5° from the normal value [femoro-tibial angle (FTA) 175°]).

PMDA determined that the modifications to the Indications or Performance and the Precautions Concerning Indications or Performance proposed by the applicant were acceptable.

6.R.5 Clinical positioning and eligible patients for JACC therapy

The applicant's explanation about the clinical positioning of JACC:

The standard drug therapy for knee OA is symptomatic treatment with HA products or NSAIDs. Surgical therapy for relatively mild knee OA is arthroscopic radical dissection (debridement), which is not curative treatment. Advanced knee OA is treated by high tibial osteotomy or knee replacement (*Rigakuryoho Kagaku.* 2005;20:235-40). However, high tibial osteotomy, which requires a non-degenerate cartilage surface, may cause degeneration of the cartilage tissue of that surface, which has become a new weight-bearing surface, over time. Knee replacement requires exercise restrictions since heavy loads on the knee may damage the artificial joint. None of the conventional therapies for knee OA provides curative treatment. A new therapy is needed.

The results of Study J-TEC 002-3 demonstrated the superiority of JACC to the HA product in the change in WOMAC score [Section 6.R.2]. The application for the previously approved indications was based on Study J-TEC 002. Its follow-up research "Follow-up of the clinical study of ACC-01 (autologous cultured cartilage) in articular cartilage defects" was conducted to evaluate the long-term outcomes of the subjects who participated in this study. This research included 3 subjects with knee OA. These subjects maintained good condition in their treated knees beyond Year 5 as confirmed by MRI scans and functional evaluation.

In summary, JACC has a different mechanism of action from those of existing symptomatic treatment and surgical therapies. JACC can be positioned as a new promising therapy that improves clinical symptoms and has a long-term effect.

PMDA's view:
It remains unclear whether JACC prevents disease progression in a long term in patients with knee OA eligible for JACC therapy based on the results of Study J-TEC 002-3 in knee OA. The study, however, demonstrated the superiority of JACC to the conventional therapy in the control group in efficacy (WOMAC score), histological improvement, etc. It is possible to position JACC as a new therapeutic option for treatment of knee OA.

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

The dosage regimen in Study J-TEC 002-3 was the same as the approved Dosage and Administration, which is also proposed in the present application for the new indication.

The applicant's explanation about the justification of the Dosage and Administration or Method of Use of JACC:
Study J-TEC 002-3, which was conducted using the approved Dosage and Administration or Method of Use, demonstrated the efficacy and safety of JACC. JACC can be manufactured, regardless of the patient's underlying disease. For these reasons, the approved Dosage and Administration or Method of Use was selected for knee OA.

On the basis of the discussion in Sections "6.R.2 Efficacy" and "6.R.3 Safety," PMDA considered it reasonable to select the approved Dosage and Administration of JACC, which was also used in Study J-TEC 002-3, for knee OA. PMDA also considers it important to appropriately provide relevant information regarding the transplantation procedures of JACC to healthcare professionals.

6.R.6.1 Multiple transplantation of JACC

PMDA asked the applicant to explain the possibility of multiple transplantation of JACC.

The applicant's response:
Patients may receive the JACC therapy more than once, e.g., re-transplantation at the same site on the ipsilateral knee joint, transplantation at different sites on the ipsilateral knee joint, and transplantation at the contralateral knee joint.

As for the safety of multiple transplantation of JACC, the possibility that ingredients remaining in JACC increase the risk of allergy cannot be fully ruled out. Since there is only limited experience with multiple transplantation of JACC, the risk of allergy is warned in the Precautions section of the package insert.

PMDA's view on multiple transplantation of JACC:
The efficacy and safety of multiple transplantation of JACC were not evaluated in Study J-TEC 002-3 and currently remain unknown. Therefore, the applicant should continue to provide the information that the efficacy and safety of multiple transplantation of JACC are unknown in the Precautions section and appropriately collect relevant information regarding multiple transplantation, if any, in the post-marketing setting.

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

The applicant's explanation about the post-marketing use-results survey plan of JACC:
The applicant plans to conduct a post-marketing surveillance covering all patients treated with JACC to evaluate the safety and efficacy of JACC in clinical use after the market launch. Graft delamination is defined as a significant adverse event (safety endpoint). According to the results of market research by the applicant, approximately [redacted] patients per year are expected to receive the JACC therapy. Assuming that approximately 300 patients are enrolled in the post-marketing surveillance at contract medical institutions between immediately after JACC is put on the market and 108 weeks before the end of the re-examination period, the planned sample size is 300. Given that the incidence of graft delamination is 3.8% (1 of 26 subjects), which is the same as that in the study, the sample size of 300 is large enough to estimate the incidence of graft delamination with a two-sided 95% confidence interval of <5%.

The applicant proposed a follow-up period of 52 weeks post-transplant for the following reasons:

- Study J-TEC 002, which was included in the application for the approved indications, demonstrated the efficacy and safety of JACC in patients with osteochondritis dissecans or traumatic cartilage defects at Week 52, as well as suggested the efficacy and safety in patients with knee OA.
- Study J-TEC 002-3 verified the superiority of JACC to the HA product in therapeutic efficacy at Week 52. Assessment by the data monitoring committee confirmed repair by hyaline cartilage-like tissue at Week 52. No problematic adverse event was reported.

Table 14. Post-marketing surveillance plan (draft)

Objective	To evaluate the safety and efficacy of JACC in clinical use after the market launch
Planned sample size	All patients diagnosed with the target disease who receive intradermal tests during the enrollment period
Target disease	Knee OA
Planned number of medical institutions	All medical institutions where JACC is used
Survey method	All-case surveillance
Survey period	Enrollment period Up to 108 weeks before the end of the re-examination period Observation period From the day of enrollment until 52 weeks after transplantation of cultured cartilage
Survey items	Safety 1) Incidence of adverse events 2) Incidence of malfunctions 3) Incidence of significant adverse events 4) Incidence of significant adverse drug reactions Significant adverse event 1) Graft delamination Significant adverse drug reactions 1) Allergic symptoms for which a causal relationship to the cultured cartilage cannot be ruled out 2) Unexplained and unknown infections for which a causal relationship to the cultured cartilage cannot be ruled out Efficacy Main survey item: Change in LKS from pre- to post-treatment with autologous cultured cartilage JACC Secondary survey items: 1) LKS 2) KOOS 3) ICRS rating score Others 1) Concomitant medications/therapies 2) K-L grade 3) Lower limb alignment[a)] 4) Reasons for discontinuation 5) Overall assessment

a) For assessment, % mechanical axis (MA) will be determined from standing frontal X-ray images of the contralateral knee.

The applicant selected the investigator-assessed LKS rating scale, not the patient-based WOMAC scoring system, among the rating systems for knee symptoms of knee OA as the main survey item for efficacy in the post-marketing surveillance because physicians can perform the assessment during clinical practice.

PMDA's view on the proposed post-marketing surveillance plan:
Since there is only very limited experience with JACC in the treatment of knee OA, the applicant's policy of the use-results survey involving all patients who receive intradermal tests after JACC is put on the market is reasonable in order to collect the safety and efficacy data of JACC in a prompt and unbiased manner. Survey items should be selected so that data can be compared with the efficacy results from the study. The duration of the follow-up period should be 104 weeks post-transplant, in view of adverse events occurring at Week 53 or later such as graft delamination that were revealed in the use-results survey for the approved indications or performance as well as the importance of long-term efficacy/safety evaluation after transplantation of JACC. Patient data should be appropriately collected for evaluation from those who require JACC transplantation more than once, if any, such as their clinical courses leading to multiple transplantation. The post-marketing surveillance plan will be finalized taking account of comments raised in the Expert Discussion.

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

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

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

8.2 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 presented in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that JACC has a certain degree of efficacy in improving clinical symptoms of knee OA, and that JACC has acceptable safety in view of its benefits. JACC available in clinical practice is meaningful because it provides a new therapeutic option for the treatment of knee OA.

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

Review Report (2)

March 28, 2025

Product Submitted for Approval

Brand Name	JACC
Non-proprietary Name	Human (autologous) cartilage-derived tissue
Applicant	Japan Tissue Engineering Co., Ltd.
Date of Application	June 17, 2024

List of Abbreviations
See Appendix.

1. Content of the Review

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

1.1 Efficacy

As a result of the review in Section "6.R.2 Efficacy" of the Review Report (1), PMDA has concluded that JACC was shown to have a certain degree of efficacy in patients with knee OA. Because Study J-TEC 002-3 provided data only up to Week 52, long-term efficacy data from Week 53 onward should be collected from patients with knee OA in the post-marketing setting.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. The following comments were also raised from the expert advisors:

- In Study J-TEC 002-3, the mean screening WOMAC score (SD) was 30.49 (±14.37) in the JACC group, which was higher than 19.57 (±9.89) in the control group. The higher screening WOMAC score may be associated with greater changes in Week 52 WOMAC score, which might have led to the overestimation of the efficacy of JACC.

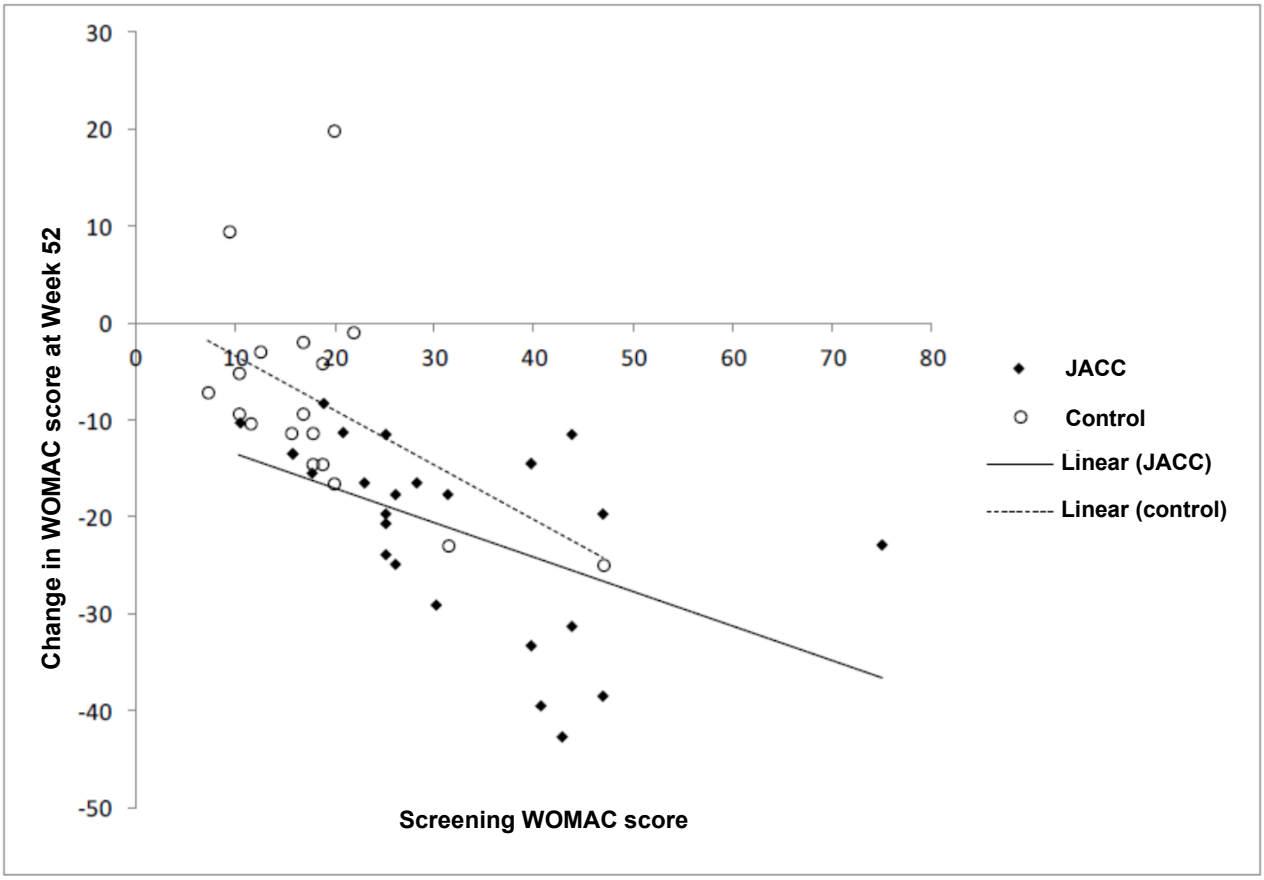
PMDA's view:
As shown in the scatter plot of Figure 1, the possibility cannot be ruled out that the difference in screening WOMAC score affected the change in score. Even so, the between-group difference at screening does not deny the efficacy results of JACC in Study J-TEC 002-3 for the following reasons:

- As mentioned in Section 6.R.2.2, the between-group difference [95% CI] in the change in Week 52 WOMAC score estimated using a multiple regression model with the screening WOMAC score and

each group as covariates was -11.69 [-17.63, -5.75]. The difference was statistically significant as in the primary analysis ($P = 0.0002$, Wald test).

- The subgroup analysis based on screening WOMAC score [5)] showed a tendency of greater improvement in score in the JACC group than in the control group in all subgroups.

Figure 1. Scatter plot of screening WOMAC score and the change in WOMAC score at Week 52 (FAS)



1.2 Safety

As a result of the review in Section "6.R.3 Safety" of the Review Report (1), PMDA has concluded that the risk associated with JACC transplantation is acceptable as long as healthcare professionals are appropriately informed of adverse events reported in Study J-TEC 002-3, etc. via materials, and, based on information provided, adverse event monitoring/management and other necessary measures are taken by physicians with adequate knowledge and experience in treatment of knee OA.

However, long-term safety data of patients with knee from OA Study J-TEC 002-3 are available only up to Week 52. In light of the adverse events observed after JACC transplantation for the approved indications or performance (traumatic cartilage defects or osteochondritis dissecans) from Week 53 onward, the applicant should appropriately obtain post-marketing long-term data even at Week 53 post-

[5)] In the subgroup analysis conducted in 2 groups based on screening WOMAC score (<30 or ≥30), the mean change (SD) at Week 52 was -5.26 (±5.75) in the JACC group and -4.59 (±9.64) in the control group in the <30 subgroup, and -27.39 (±10.72) in the JACC group and -8.63 (±17.90) in the ≥30 subgroup. In the subgroup analysis in 2 groups based on screening WOMAC score (<20 or ≥20), the mean change (SD) at Week 52 was -10.92 (±4.20) in the JACC group and -4.51 (±9.86) in the control group in the <20 subgroup, and -23.24 (±9.61) in the JACC group and -6.80 (±13.55) in the ≥20 subgroup.

transplant and later and advise caution to healthcare professionals promptly once any adverse events of concern are identified.

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

1.3 Clinical positioning, indication(s), or performance

As a result of the review in Sections "6.R.4 Indications or performance" and "6.R.5 Clinical positioning and eligible patients for JACC therapy" of the Review Report (1), PMDA has concluded that the Indications or Performance and the Precautions Concerning Indications or Performance of JACC should be defined as per the respective sections.

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

1.4 Dosage and administration or method of use

As a result of the review in Section "6.R.6 Dosage and administration or method of use" of the Review Report (1), PMDA has concluded that the descriptions of the approved Dosage and Administration or Method of Use of JACC are also applicable to the additional indication. Meanwhile, Study J-TEC 002-3 did not evaluate the efficacy and safety in patients undergoing JACC transplantation more than once. The Precautions section, etc. should continue to inform that the efficacy and safety remain unknown in multiple transplantation of JACC in patients with knee OA, and information about such cases, if any, should be collected in the post-marketing setting appropriately.

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

1.5 Post-marketing surveillance plan (draft)

The applicant proposed a post-marketing surveillance plan covering all patients treated with JACC, with a follow-up period of 52 weeks post-transplant, to evaluate the safety and efficacy of JACC in post-marketing clinical use.

In Section "7 Risk Analysis and Outline of the Review Conducted by PMDA" of the Review Report (1), the re-examination survey pertaining to the approved indications or performance revealed adverse events such as graft delamination observed even at Week 53 post-transplant or later, indicating the importance of long-term efficacy/safety evaluation after JACC transplantation in patients with knee OA. Thus, PMDA considers that the recommendable follow-up period is 104 weeks post-JACC transplantation.

The PMDA's conclusion was supported by the expert advisors at the Expert Discussion. The following comments were also raised from the expert advisors:

- In view of the importance of the long-term outcomes with JACC, the use of data cut-off, etc. should also be considered for patients early enrolled in the survey, rather than requiring 104-week post-transplant follow-up for all cases, so that longer-term data can be obtained.
- The main efficacy survey item should be a patient-based clinical function score, not LKS.

Taking account of opinions from expert advisors, PMDA asked the applicant to re-discuss the survey period and the main efficacy survey item, and the applicant presented the post-marketing surveillance plan (draft) shown in Table 15. PMDA concluded that the modified plan was appropriate.

Table 15. Post-marketing surveillance plan (draft)

Objective	To evaluate the safety and efficacy of JACC in post-marketing clinical use
Planned sample size	All patients diagnosed with the target disease who receive intradermal tests during the enrollment period
Target disease	Knee OA
Planned number of medical institutions	All medical institutions providing JACC treatment
Survey method	All-case surveillance
Survey period	Enrollment period: From the approval date until Month 23 post-approval date Observation period: From the day of enrollment until the data cut-off date for re-examination Data cut-off date: 36 months post-approval date
Survey items	Safety: 1) Incidence of adverse events 2) Incidence of malfunctions 3) Incidence of significant adverse events 4) Incidence of significant adverse drug reactions Significant adverse event 1) Graft delamination Significant adverse drug reactions 1) Allergic symptoms for which a causal relationship to the cultured cartilage cannot be ruled out 2) Unexplained and unknown infections for which a causal relationship to the cultured cartilage cannot be ruled out Efficacy Main survey item: Change in KOOS from baseline to Week 52 post-transplant with JACC autologous cultured cartilage Secondary survey items: 1) KOOS 2) LKS 3) ICRS rating score Others 1) Concomitant medications/therapies 2) K-L grade 3) Lower limb alignment[a)] 4) Reasons for discontinuation 5) Overall assessment

a) Assessed based on %MA determined from standing frontal X-ray images of the target knee.

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

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

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

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

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

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the modified proposed indications or performance and the dosage and administration or method of use below with the following conditions, if the provision of cautionary advice via the package insert and the dissemination of information about proper product use are fulfilled in the post-marketing setting. The present application only pertains to the additional indications or performance of the approved regenerative medical product, and thus the re-examination period for the indication or performance in the present application should be 4 years.

Indications or Performance

1. Traumatic cartilage defects or osteochondritis dissecans

   Alleviation of clinical symptoms of traumatic cartilage defects or osteochondritis dissecans of the knee exclusively with a cartilage defect measuring 4 cm^2 or larger for which there are no other treatment options

2. Knee osteoarthritis

   Improvement of clinical symptoms of knee osteoarthritis exclusively with a cartilage defect measuring 2 cm^2 or larger which do not respond to exercise therapy or other conservative therapies

(Underline denotes additions.)

Dosage and Administration or Method of Use

1. Transplantation planning
   (1) The marketing authorization holder sends the designated form to the treating physician upon request.
   (2) The treating physician performs pre-procedural testing, namely, beef allergy test for allergy to bovine serum and atelocollagen intradermal test for allergy to bovine dermis-derived collagen. The intradermal test is performed at least 4 weeks prior to transplantation of cultured cartilage (see 2. Intradermal test). If the result of the beef allergy or intradermal test turns out positive, the patient is ineligible for the use of the cultured cartilage, and the cultured cartilage must not be transplanted. Judgment method: the patient is instructed to carefully observe the test site for 4 weeks and report any abnormal reaction during this period. If adverse events or unexpected unknown abnormal reactions such as swelling, redness, itchy feeling, induration, and pyrexia occur, the result of the intradermal test is determined to be positive.
   (3) In the designated form, the treating physician fills in necessary information including the number of cultured cartilage required and dates of tissue harvest and transplantation scheduled, and requests the production of JACC.

(4) Up to 2 pieces each of JACC templates and JACC collagen patches are packed in one package depending on the necessary number of cultured cartilage, recipient site, shape of the recipient site, etc.
(5) A patient-specific code is issued for each transplantation plan for identification.

2. Intradermal test (at least 4 weeks prior to transplantation of cultured cartilage)
(1) Open the package of atelocollagen for intradermal test. Take out the package content, holding the glass syringe with fingers.
(2) Remove the rubber stopper, and securely screw the injection needle into the Luer-lock.
(3) Remove the injection needle cap by pulling it straight out so that the needle tip is not damaged.
(4) Push the plunger slowly to inject approximately 0.1 mL of atelocollagen into the forearm subcutaneously.

3. Sending the tissue transport set
The manufacturer sends the tissue transport set to the medical institution for tissue harvest. The set consists of a tissue transport tube and a blood storage tube. Harvested tissue is stored in a special heat-insulated container for transportation.

4. Tissue harvest
Healthy cartilage tissue must be harvested from the knee joint. The treating physician arthroscopically determines the harvest site where there is no risk of functional impairment after harvest, such as a non-weight-bearing site in the femoral medial or lateral condyle, according to the standard arthroscopic procedure. Tissue is harvested from the superficial to deep layers of the cartilage using a grooved chisel, ring curette, etc. for ear operation with a 3 to 7 mm blade. Approximately 0.4 g of cartilage tissue is harvested. A loose body in the joint must not be harvested.

5. Storage of harvested tissue at medical institution
(1) Open the outer box of the tissue transport tube in a clean environment (e.g., surgical room and treatment room). Check the tissue transport tube for leakage and turbidity of the tissue transport liquid in the tube. The tube should not be tilted or shaken excessively.
(2) Uncap the tissue transport tube. In a clean environment, bring the harvested cartilage tissue using sterile tweezers, etc. to be immersed in the tissue transport liquid in the tube. Cap the tube tightly to prevent a leak of the liquid.
(3) Collect blood according to the standard procedure. Store the collected blood in the blood storage tube.
(4) To prevent mix-up, label the tissue transport tube, blood storage tube, and the designated form with the patient-specific code.

6. Transportation of harvested tissue
The tissue transport tube and blood storage tube containing the collected blood are placed back into the outer box, which is then sealed with a sticker and placed in the heat-insulated transport container. The container is sealed at 4 spots with sealing bands and sent back to the manufacturer (transport temperature, 2°C-20°C). The expiration date (the duration for temperature control capability),

which is clearly indicated on the heat-insulated transport container provided by the manufacturer, must be strictly observed.

7. Acceptance inspection and handling of the product at medical institution
   (1) The package of cultured cartilage is transported in a heat-insulated transport container sealed with sealing bands. Upon the arrival of the package, the medical institution must ensure that the heat-insulated transport container is sealed. If the sealing is broken, the package should not be opened, and the medical institution should contact the marketing authorization holder.
   (2) Cut the sealing bands of the heat-insulated transport container and take out the package of cultured cartilage.
   (3) Cross-check the tissue code on the transport container against the designated form kept at the medical institution, and check the quantity of the contents.
   (4) Visually check the transport container for cracks, chips, and leakage, and turbidity and foreign matters in the transport liquid. Store at 8°C to 25°C until immediately before use. If any of these abnormalities is identified, the cultured cartilage must not be used.
   (5) The cultured cartilage should be transplanted before the expiration date written on the transport container. Expired products must not be used.

8. Pre-transplantation check
   Take out the multipurpose dish, with the cultured cartilage on it, from the transport container and place it in a clean area. When taking out the cultured cartilage from the container, double-check the transport liquid for turbidity or foreign matters. Cultured cartilage must not be used in case the transport liquid is turbid or contaminated.

9. Transplantation procedure (example)
   (1) Expose the defect site according to the standard surgical procedure.
   (2) Debride the degenerative cartilage, etc. at the defect site to expose the subchondral bone.
   (3) Debride the degenerative cartilage, etc. around the defect site so that the recipient site is clear.
   (4) Shape the JACC template, etc. as necessary to fit the recipient site.
   (5) Place a fixation patch (either the JACC collagen patch or periosteal patch) over the recipient site to anchor the cultured cartilage according to the following procedures:
      1) With JACC collagen patch
         Cut the JACC collagen patch into the shape and size of the shaped JACC template, etc. and immerse the patch in Ringer's solution, physiological saline, etc., allowing it to swell. Place the JACC collagen patch over the recipient site with its porous surface on the bone side.
      2) With Periosteal patch
         From the surface of the proximal anteromedial tibia, harvest a periosteal patch in a size slightly larger than the shaped JACC template, etc. Place the patch over the recipient site with its osteogenetic layer touching the joint surface.
   (6) Suture the fixation patch halfway around the perimeter to the surrounding cartilage. Stitches should be approximately 3 mm apart.

(7) Take out the cultured cartilage and trim it as necessary using the shaped JACC template, etc. to fit the recipient site. Insert the cultured cartilage between the recipient site and the fixation patch with its flat surface on the bone side.
(8) Suture the fixation patch around the remaining half of perimeter to the surrounding cartilage. Separately, fix the fixation patch by the pull-out method.
(9) Ensure that there is no detachment of the fixation patch or leakage of the cultured cartilage when bending and stretching the knee. Close the wound according to the standard surgical procedure.

(No change)

Approval Conditions

1. The applicant is required to take necessary measures, such as disseminating the guidelines for proper use jointly prepared with relevant academic societies and offering seminars, to ensure that the product is used for eligible patients selected, by physicians and at medical institutions with adequate knowledge and experience in the treatment of knee osteoarthritis and a good understanding of the product's efficacy and safety.
2. Because of the extremely limited number of the clinical study participants, the applicant is required to conduct a use-results survey covering all patients treated with the product, until the end of the re-examination period in principle, to understand the characteristics of patients treated with the product, collect product safety/efficacy data promptly, and take necessary measures to ensure its proper use.

Appendix

List of Abbreviations

ADL	Activities of daily living
Application	Application for marketing approval
BMI	Body mass index
CI	Confidence interval
DVT	Deep vein thrombosis
FAS	Full analysis set
FTA	Femoro-tibial angle
HA	Sodium hyaluronate
ICRS	International Cartilage Repair Society
JACC	JACC
K-L	Kellgren-Lawrence
Knee OA	Knee osteoarthritis
KOOS	Knee injury and Osteoarthritis Outcome Score
LKS	Lysholm Knee Score
LOCF	Last Observation Carried Forward
MA	Mechanical Axis
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MOCART	Magnetic Resonance Observation of Cartilage Repair Tissue
MRI	Magnetic Resonance Imaging
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
QOL	Quality of life
PMDA	Pharmaceuticals and Medical Devices Agency
SNRI	Serotonin Noradrenaline Reuptake Inhibitor
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index