December 16, 2021
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Adipose tissue separation kit
Brand Name	Celution Cell Therapy Kit SUI
Applicant	Cytori Therapeutics, K.K.
Date of Application	December 24, 2019 (Application for marketing approval)

Results of Deliberation

In its meeting held on December 16, 2021, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product should be approved as a medical device that requires a use-results survey. The product is not classified as a biological product or a specified biological product.

The use-results survey period should be 5 years.

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

Review Report

August 6, 2021

Pharmaceuticals and Medical Devices Agency

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

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Adipose tissue separation kit
Brand Name	Celution Cell Therapy Kit SUI
Applicant	Cytori Therapeutics, K.K.
Date of Application	December 24, 2019
Reviewing Office	Office of Medical Devices II

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Review Results

August 6, 2021

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Adipose tissue separation kit
Brand Name	Celution Cell Therapy Kit SUI
Applicant	Cytori Therapeutics, K.K.
Date of Application	December 24, 2019

Results of Review

Celution Cell Therapy Kit SUI is a single-use kit consisting of an adipose tissue collection container, a processing chamber, a waste bag, a tubing set, and an enzyme (Celase). The product is used in combination with a centrifuge to separate stromal stem cells from adipose tissue (approximately 250-300 mL) collected from the patient. The separated stromal stem cells are used for the treatment of male stress urinary incontinence. A total of 1 mL of separated stromal stem cells is injected into both sides of the external urethral sphincter, followed by a submucosal injection of a mixture of stromal stem cells (4 mL) and adipose tissue (16 mL), 20 mL in total, into both sides of the membranous urethral mucosa. The components of Celution Cell Therapy Kit SUI are the same as those of Celution Cell Therapy Kit (Approval number 23000BZX00357000) (hereinafter referred to as the applicant's approved product).

The applicant submitted non-clinical data from efficacy and safety studies of stromal stem cells in animals and cells. Biological safety, stability and durability, and the performance and stromal cell yield of the disposable set were not evaluated with Celution Cell Therapy Kit SUI because they are the same as those of the applicant's approved product.

The applicant submitted clinical data from a pivotal study that evaluated the efficacy and safety of Celution Cell Therapy Kit SUI.

The pivotal study was a multicenter, prospective, open-label, uncontrolled study involving 45 patients. The primary efficacy endpoint was "the percentage of patients achieving a 50% reduction in urine leakage amount from baseline to Week 52 measured by a 24-hour pad test (responders)." The percentage of responders in this study was [redacted]%, achieving the pre-specified threshold. There were no adverse events for which a causal relationship to the investigational device could not be ruled out. Two adverse events for which a causal relationship to "a mixture of adipose tissue and stromal stem cells" or "stromal stem cells" could not be ruled out occurred in 2 patients. A total of 39 adverse events for which a causal relationship to the study procedure could not be ruled out occurred in 36 patients. All these events resolved or were resolving. In addition, a serious embolism occurred in 1 patient. The event was likely associated with the prolonged entire surgery time due to more time consumed in liposuction than expected. Therefore a causal relationship to Celution Cell Therapy Kit SUI, the study procedure or to

the injectable collected with Celution Cell Therapy Kit SUI was ruled out. Nevertheless, embolism occurred in a series of surgical operations for the treatment with Celution Cell Therapy Kit SUI, and given this, safety measures against embolism will be provided to healthcare professionals.

As a result of its comprehensive review of the submitted data based on the conclusions at the Expert Discussion, PMDA concluded that the data support the efficacy of Celution Cell Therapy Kit SUI and its safety is acceptable. However, in view of no other medical device for stromal stem cell separation used in the treatment of male stress urinary incontinence in Japan, and of a series of unique procedures the product requires, a use-results survey should be conducted in the post-marketing setting to verify the product's efficacy and safety in clinical use. In addition, considering the characteristics of the product, appropriate selection of eligible patients and surgical procedures, etc. are important to ensure the efficacy and safety of the product. Given the necessary actions expected to be taken including adherence to the guidelines for proper use provided by academic societies concerned, holding seminars, etc., the following approval conditions should be attached.

As a result of its review, PMDA has concluded that Celution Cell Therapy Kit SUI may be approved for the intended use shown below with the following approval conditions, and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use

Celution Cell Therapy Kit SUI is a single-use special kit to separate, clean, and process adipose tissue by centrifugation to obtain specific cells or tissue to be administered to patients with mild to moderate stress urinary incontinence associated with urethral sphincter incompetence secondary to a surgery for prostatic hyperplasia or prostate cancer who have no or inadequate response to behavioral and drug therapies.

Approval Conditions

1. The product should be used by surgeons with adequate knowledge and experience in the treatment of male lower urinary tract symptoms who have acquired competent skills for the use of the product and knowledge about procedure-associated complications, and at medical institutions with a well-organized care system. To fulfill these requirements, the applicant is required to take any necessary measures in cooperation with academic societies concerned.
2. The applicant is required to disseminate the guidelines for proper use developed by academic societies concerned, hold seminars, and take other necessary measures.
3. The applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, submit the results of interannual analyses to the Pharmaceuticals and Medical Devices Agency, and take other appropriate measures as necessary.

Review Report

August 6, 2021

Product for Review

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Adipose tissue separation kit
Brand Name	Celution Cell Therapy Kit SUI
Applicant	Cytori Therapeutics, K.K.
Date of Application	December 24, 2019
Proposed Intended Use	Celution Cell Therapy Kit SUI is a single-use special kit to separate, clean, and process adipose tissue by centrifugation to obtain specific cells or tissue for the treatment of patients with male stress urinary incontinence.

Table of Contents

List of Abbreviations

FAS	Full Analysis Set
ICIQ-SF	International Consultation on Incontinence Questionnaire-Short Form
KHQ	King's Health Questionnaire
PSA	Prostate Specific Antigen
QOL	Quality of Life
SUI	Stress Urinary Incontinence

I. Product Overview

Celution Cell Therapy Kit SUI is a single-use kit consisting of an adipose tissue collection container, a processing chamber, a waste bag, a tubing set, and an enzyme ([redacted], called "Celase") (Figure 1). The product is used in combination with a centrifuge[i] to separate stromal stem cells[ii] from adipose tissue (approximately 250-300 mL) collected from the patient. Separated stromal stem cells are used in the treatment of male stress urinary incontinence (SUI). A total of 1 mL of stromal stem cells is injected into both sides of the external urethral sphincter, followed by a submucosal injection of a mixture of stromal stem cells (4 mL) and adipose tissue (16 mL), 20 mL in total into both sides of the membranous urethral mucosa (Figures 2 and 3). The isolation of stromal stem cells from adipose tissue requires no incubation process. The components of the product are the same as those of the approved product "Celution Cell Therapy Kit" (Approval number 23000BZX00357000) (hereinafter referred to as the applicant's approved product)[iii] and are used in the same manner as that for the applicant's approved product up to the adipose tissue isolation step. Because the approved product has no specific indication, this marketing approval application for Celution Cell Therapy Kit SUI has been submitted for a new indication of male SUI.

Figure 1 shows the exterior of the components of Celution Cell Therapy Kit SUI. Figure 2 shows the flow diagram of the entire treatment process using the product. Figure 3 shows how stromal stem cells, etc. are administered transurethrally to the affected site.

[i] "Celution Centrifuge" (13B1X10155000001), the company's registered product is used

[ii] Stromal stem cells in stromal vascular fraction in adipose tissue are also called "adipose-derived regenerative cells (ADRCs)." ADRCs in Figures 2 and 3 refer to stromal stem cells.

[iii] Intended use: Celution Cell Therapy Kit is a special kit to separate, clean, and process adipose tissue by centrifugation to obtain specific cells or tissue to be administered. Celution Cell Therapy Kit is intended for a single use.

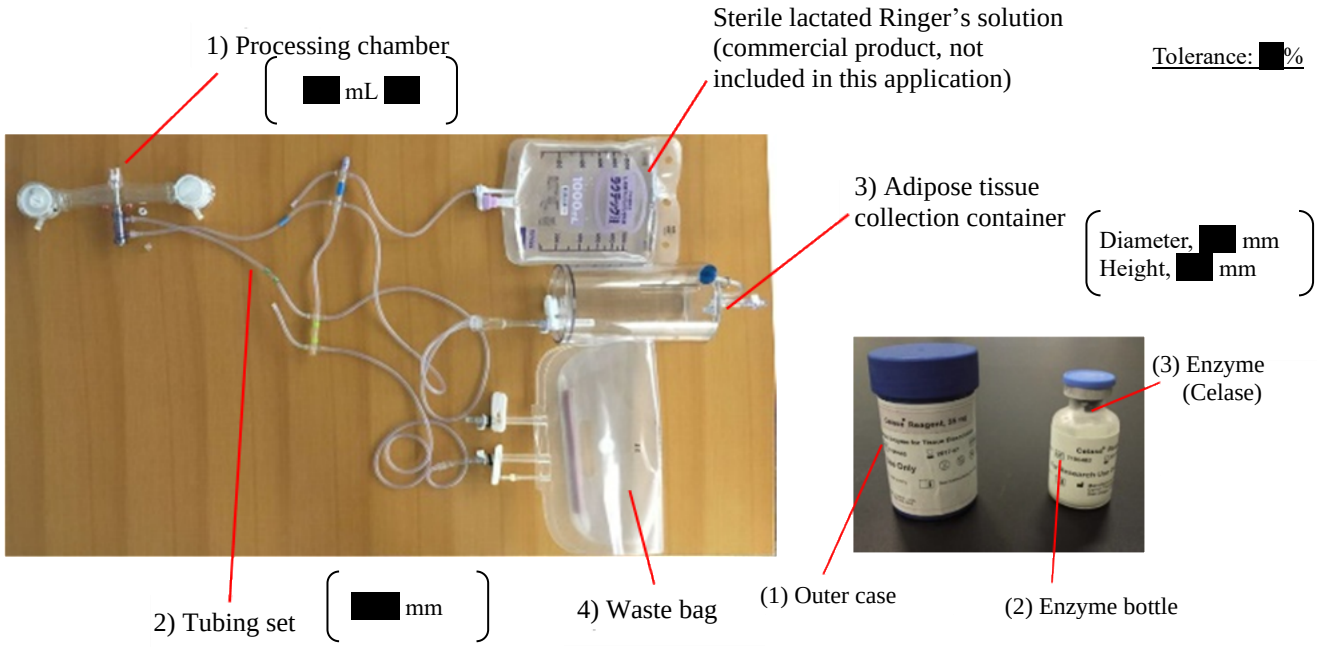


Figure 1. Exterior appearance of Celution Cell Therapy Kit SUI

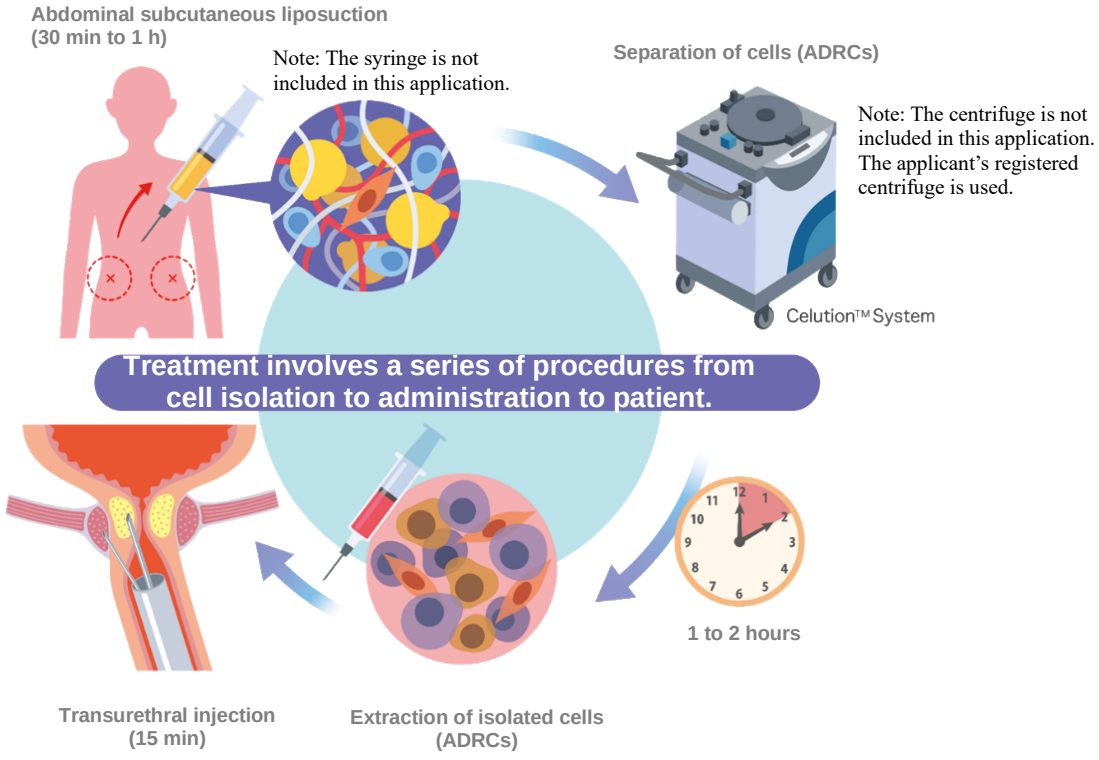
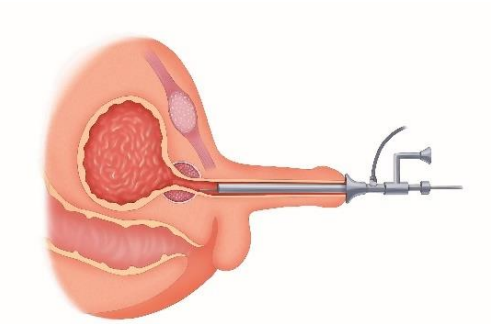
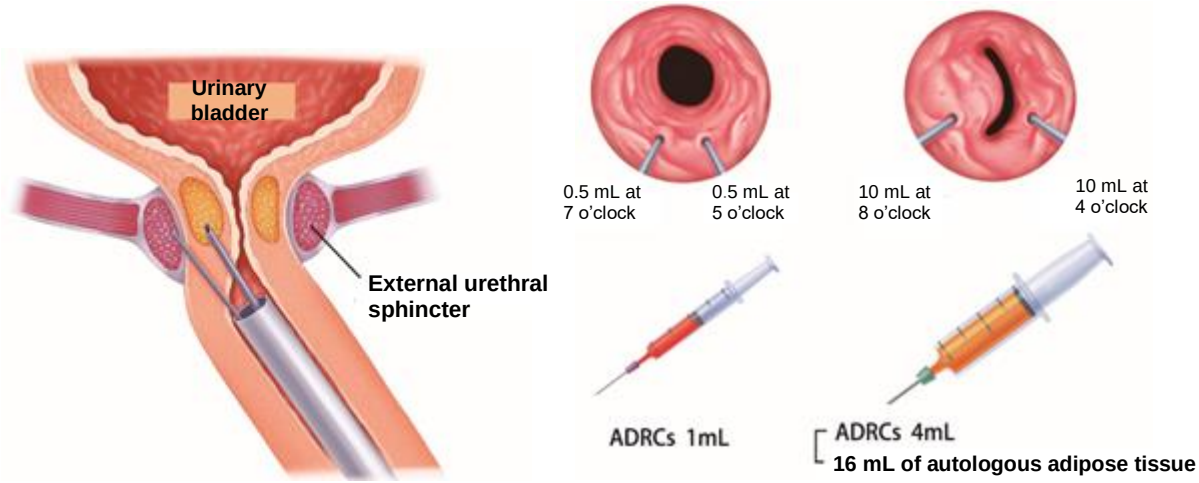


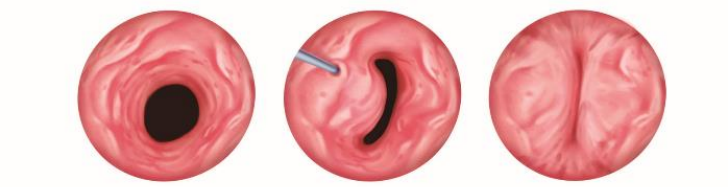
Figure 2. Flow diagram of the entire treatment with Celution Cell Therapy Kit SUI



Insertion of endoscope



Transurethral endoscopic injection of stromal stem cells and adipose tissue



Closure of urethral sphincter by injection

Figure 3. Transurethral injection

II. Summary of the Data Submitted and Outline of the Review Conducted by the Pharmaceuticals and Medical Devices Agency

The data submitted for the present application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors present during the Expert Discussion on Celution Cell Therapy Kit SUI declared that they did not fall under Item 5 of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8 dated December 25, 2008).

1. History of Development, Use in Foreign Countries, and Other Information

1.A Summary of the data submitted

1.A.(1) History of development

Urinary incontinence is broadly classified into 4 types based on clinical symptoms, i.e., stress incontinence, urge incontinence, overflow incontinence, and functional incontinence. SUI, for which the product is indicated, refers to an involuntary leakage of urine occurring without bladder contractions during moments of physical activity that increases abdominal pressure, such as exertion/exercising, coughing, sneezing. This type of urinary incontinence is most common in women with pelvic floor muscle relaxation or urethral sphincter incompetence due to pregnancy, child delivery, or aging. Men tend to have overflow incontinence caused by a lower urinary tract obstruction owing to prostatic hypertrophy more often rather than SUI. Articles report about the benefits of treatment of SUI in more cases in women than men. Male SUI results from neurogenic bladder or traumatic injury associated with spina bifida, or occurs as a complication of a surgery for prostatic hyperplasia or prostate cancer. As mentioned, however, limited clinical data and treatment options are available for SUI in men as compared with that in women. Furthermore, refractory SUI persisting for ≥1 year after prostate cancer surgery is hardly likely to improve rapidly.[1)]

The current major treatment options for male SUI in Japan are behavioral therapy, drug therapy, and surgical therapy. Behavioral or drug therapy is often the first-choice treatment. However, these primary therapies may not work for SUI associated with urethral sphincter incompetence secondary to a prostate surgery. For patients who have an inadequate response to these therapies, a surgical therapy with an artificial urethral sphincter (medical device) is considered for urination control. Artificial urethral sphincter implantation however requires many components including a pressure balloon, a cuff, and a control pump to be placed in the body for life, and is thought to be the last option. Implantation is a highly invasive surgical procedure with a risk of infection, etc. and may require re-implantation of replacements for worn components, etc. For this reason, in Japan, artificial urethral sphincter implantation is predominantly indicated for severe urinary incontinence. In the past, periurethral collagen injection was also a treatment option. This option is however no longer available because of the discontinuation of relevant products, leaving artificial urethral sphincter implantation as the only surgical treatment option in Japan at present. There is no other treatment option for patients with (mainly mild to moderate) SUI inadequately responding to behavioral or drug therapy who do not use an artificial urethral sphincter. Inevitably, these patients need to cope with involuntary urine leakage triggered by physical movements in daily activities, with the use of bladder control pads all the time, which restricts their activities and significantly decreases their quality of life (QOL).

Given this current situation in the treatment of male SUI, the clinical application of Celution Cell Therapy Kit has been studied in men with mild to moderate SUI who have an inadequate response to behavioral and drug therapies. A new marketing approval application was submitted with the proposed brand name of Celution Cell Therapy Kit SUI. "SUI" stands for stress urinary incontinence.

With the product, approximately 250 to 300 mL of subcutaneous adipose tissue is aspirated from the patient, from which stromal stem cells are isolated and processed. Processed stromal stem cells and adipose tissue are injected into the periurethral area of the patient to help improve the symptoms of male SUI. As shown in Figures 2 and 3, a 20-mL mixture of stromal stem cells (4 mL) and adipose tissue (16 mL) is injected submucosally into both sides of the membranous urethra. The injection, causing the injection sites to be bulged, is expected to increase urethral resistance. Based on the reported volume of adipose tissue injected periurethrally alone, 12 to 21 mL, for the treatment of SUI,[2)] a 20-mL mixture is within the reported volume range. The transurethral endoscopic injection allows the closure of the urinary tract to be visually observed.

Stromal stem cells used in the treatment are those included in the stromal vascular fraction in adipose cells. Those stromal stem cells are known to have the ability to differentiate themselves into a variety of cell lineages including adipose cells and blood vessels.[3)] The injection of 1 mL of stromal stem cells into both sides of the external urethral sphincter is expected to lead to the regeneration of the external urethral sphincter, a smooth muscle.[iv]

In this treatment, the isolation of stromal stem cells from adipose tissue requires no incubation process and can be done in a short time. Adipose tissue for this treatment can be obtained by liposuction as practiced commonly in plastic surgeries.

1.A.(2) Use in foreign countries

Celution Cell Therapy Kit SUI has not been approved for the treatment of male SUI in foreign countries.

For reference, Table 1 shows the use of the applicant's approved products for different indications in foreign countries.

[iv] The results from an animal study (in pigs) suggested the regeneration of the smooth muscle. The study report was submitted as supporting data.

Table 1. Use in foreign countries

Region	Brand name	Accreditation number/ date of approval	Volume of shipments of consumables per year						
			2015	2016	2017	2018	2019	2020	2021
Europe	Celution 800/CRS Device/Celution 805/CRS Consumable Set	CE 544833 1/16/2009	[redacted]						
US	CYTORI CELUTION CELL CONCENTRATION DEVICE	K060482 9/28/2006							
Asia (other than Japan)	Celution 800/CRS Device/Celution 805/CRS Consumable Set	Singapore: 3/13/2008 Indonesia: 1/28/2009 Korea: 9/16/2009							
Others	Celution 800/CRS Device/Celution 805/CRS Consumable Set	Israel: 12/2008 Turkey: 6/2008 Ukraine: 11/5/2008							
		Total							

(Date of survey, as of the end of June 30, 2021)

The following summarizes the intended use approved for the products in Europe and the US.

Europe

The set device of Celution 800 cell processing system and Celution 805 consumables is used to digest adipose tissue, and extract, clean, and concentrate stromal stem cells and other related precursor cells to be used for autologous re-implantation or re-infusion.

The product is meant for the following plastic surgical procedures that involve replacement, repairment, reconstruction, or plumping:

- Surgical defect of soft tissue such as the breasts after mastectomy or lumpectomy (defect size, ≤150 mL; increase in volume, up to 260 mL)
- Liposuction-induced defect in the abdominal, back, thigh, buttocks, etc.
- Congenital asymmetry of soft tissue in the breasts, face, etc.
- Anatomical defect of soft tissue in the breasts, buttocks, face, etc.
- Debilitating disease of soft tissue affecting the hands or face

US

The device collects autologous cells peri- or post-operatively, concentrates and cleans the collected autologous cells to obtain concentrated blood cells for reinfusion. The device is applicable in general surgery, cardiovascular surgery, orthopedic surgery, vascular surgery, plastic surgery, gynecology and obstetrics, neurosurgery, chest surgery, transplant surgery, emergency care/traumatic injury treatment, urology, and postoperative treatment.

The number of the applicant's approved products delivered was [redacted] in Japan as of June 30, 2021.

2. Design and Development

2.(1) Performance and safety specifications

2.(1).A Summary of the data submitted

The proposed performance and safety specifications of Celution Cell Therapy Kit SUI are the same as those of the applicant's approved products as shown below. The applicant explained that the proposed

specification of [redacted] would be sufficient to ensure [redacted] that is required for the treatment, based on the results of the feasibility study[5)] submitted as reference data for this application (described in Section "6.A.(2) Clinical data submitted as reference data").

1) Performance specification: airtightness of the disposable set, tension strength of the joints, liquid injection/draining performance of the port, output volume of the chamber, [redacted] after isolation, [redacted] after isolation, [redacted], [redacted] in cell solution, and residual endotoxins in cell solution

2) Safety specification: biological safety, sterility, and ethylene oxide sterilization residuals

2.(1).B Outline of the review conducted by PMDA

PMDA reviewed the justification for performance- and safety-related specifications and standard values, and concluded that there was no particular problem with the specifications, methods, or standard values, requiring no additional specifications for this application other than those of the applicant's approved products .

2.(2) Physicochemical properties

2.(2).A Summary of the data submitted

Celution Cell Therapy Kit SUI has no function that induces a physical or chemical action. Physicochemical property data of the device were thus omitted.

2.(2).B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with the omission of physicochemical property data of Celution Cell Therapy Kit SUI.

2.(3) Electric safety and electromagnetic compatibility

2.(3).A Summary of the data submitted

This application covers only the disposable kit which does not use electricity Data on electric safety or electromagnetic compatibility were thus omitted.

2.(3).B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with the omission of the electric safety or electromagnetic compatibility data of Celution Cell Therapy Kit SUI.

2.(4) Biological safety

2.(4).A Summary of the data submitted

Celution Cell Therapy Kit SUI holds the same components as he applicant's approved product. The biological safety data of the product was thus omitted.

2.(4).B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with the omission of biological safety data of Celution Cell Therapy Kit SUI.

2.(5) Radiological safety

2.(5).A Summary of the data submitted

Celution Cell Therapy Kit SUI does not emit radiation. Radiological safety data were thus omitted.

2.(5).B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with the omission of radiological safety data of Celution Cell Therapy Kit SUI.

2.(6) Mechanical safety

2.(6).A Summary of the data submitted

Celution Cell Therapy Kit SUI does not pose a mechanical hazard. Mechanical safety data were thus omitted.

2.(6).B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with the omission of mechanical safety data of Celution Cell Therapy Kit SUI.

2.(7) Stability and durability

2.(7).A Summary of the data submitted

Celution Cell Therapy Kit SUI holds the same components as those of the applicant's approved product. Stability and durability data was thus omitted.

2.(7).B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with the omission of stability and durability data of Celution Cell Therapy Kit SUI.

2.(8) Performance

2.(8).A Summary of the data submitted

Because Celution Cell Therapy Kit SUI holds the same components as those in the applicant's approved product, performance data (e.g., airtightness and tension strength) of the disposable kit, stromal cell yield data (e.g., [redacted] and [redacted]) and efficacy and safety data of stromal stem cells were partially omitted.

The applicant submitted data on [redacted] to support the efficacy and safety of stromal stem cells required for the treatment of male SUI with Celution Cell Therapy Kit SUI. The results of this study demonstrated that the injection of [redacted], and [redacted] significantly improved [redacted] relative to [redacted]. The data also suggested that improvement in [redacted] (Table 2). On the basis of the study the results, the lower limit of stromal stem cell number to be administered to humans in the later-mentioned pivotal study was determined. The study results also indicated that sufficient volume of cells can be harvested through the standard isolation procedure.

Table 2. [redacted]

Study group	Week [redacted]			Week [redacted]		
[redacted] group ([redacted])		±			±	
[redacted] group ([redacted] group)		±			±	
Group receiving [redacted] cells		±			±	
Group receiving [redacted] cells		±			±	

Mean ± standard deviation (SD)

The applicant also submitted data regarding [redacted] and [redacted]. The results of these studies suggested [redacted], indicating the probability of [redacted]. In addition, the data suggested that [redacted] do not have [redacted].

2.(8).B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with the omission of the data on performance and stromal cell yield of the disposable kit and some data on the efficacy and safety of stromal stem cells. PMDA reviewed the efficacy and safety of stromal stem cells specific to the purpose of this application and concluded that there was no particular problem with the results of the studies.

2.(9) Directions for use

2.(9).A Summary of the data submitted

Data on the directions for use were omitted because cells isolated and processed by Celution Cell Therapy Kit SUI are administered to patients endoscopically through the urethra, which requires no further validation.

2.(9).B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with the omission of data on the directions for use of Celution Cell Therapy Kit SUI.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

3.A Summary of the data submitted

The applicant submitted the declaration of conformity declaring that Celution Cell Therapy Kit SUI meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Ministerial Announcement No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of Celution Cell Therapy Kit SUI to the Essential Principles.

(a) Conformity to Article 1, which specifies preconditions for designing medical devices, (particularly the requirements for users including the levels of technical knowledge and experience expected and the levels of education and training to be provided):

As described later in Section "6.B.(2) Post-marketing safety measures," the selection of eligible patients and users for the treatment, training of users and adherence to the guidelines for proper use

are important factors to keep the risk-benefit balance of Celution Cell Therapy Kit SUI. To this end, approval conditions need to be attached to seek the fulfillment of necessary measures.

(b) Conformity to Article 2, which specifies requirements for risk management throughout the product life cycle of medical devices:
As described later in Section "6.B. Outline of the review conducted by PMDA" and Section "7.B. Outline of the review conducted by PMDA," the treatment with Celution Cell Therapy Kit SUI is highly novel and unique from the conventional techniques, and therefore information about cases with the use of the product needs to be collected from the clinical settings. Safety and efficacy of the product should be investigated through post-marketing surveillance. Furthermore, eligibility for patients who have undergone the treatment with the product should be verified, based on which additional risk reduction measures should be taken as necessary. To seek the fulfillment of these measures, approval conditions will be attached.

(c) Conformity to Article 3, which specifies requirements for the performance and functions of medical devices, and Article 6, which specifies the efficacy of medical devices:
As described in Section "2.(8) Performance," PMDA reviewed the justification of the submitted performance data for the specifications, results, and discussions, and confirmed that the data demonstrated the appropriate performance of the product. PMDA verified the conformity of the product to Articles 3 and 6.

(d) Conformity to Article 7, which specifies requirements for the chemical properties, biological safety, etc. of medical devices:
As described earlier in Sections "2. 4. B. Outline of the review conducted by PMDA" (Biological safety) and later in Section "4.B. Outline of the review conducted by PMDA" （Risk Management）, PMDA verified that the product conforms to the requirements for its chemical properties, biological safety, etc.

(e) Conformity to Article 8, which specifies anti-microorganism contamination measures for medical devices, Article 9 specifying considerations in concurrent use with other medical devices, and Article 14 specifying considerations in the prevention of connection error of medical devices:
As described later in "4.B. Outline of the review conducted by PMDA" (Risk Management)," PMDA verified that the product conforms to the requirements for anti-microorganism contamination measures, considerations in concurrent use with other medical devices, and considerations in the prevention of connection error.

(f) Conformity to Article 17, which specifies requirements for publicizing information including precautionary advice or the communication of information to users via instructions for use, etc. (hereinafter referred to as precautions and other information):
As described later in Section "6.B.(2) Post-marketing safety measures," cooperation between urology department and plastic surgery department, accurate performance of procedures, selection of eligible patients, etc. are important to keep the risk-benefit balance of the product. The applicant needs to

provide information through precautionary advice, the guidelines for proper use to users, training, etc.

PMDA comprehensively reviewed the conformity of Celution Cell Therapy Kit SUI to the Essential Principles and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management, risk management system, and its implementation status with Celution Cell Therapy Kit SUI in accordance with ISO 14971:2007 "Medical devices – Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the document on risk management taking into account the discussion in Section "3.B. Outline of the review conducted by PMDA" and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on tests conducted during the manufacturing process of Celution Cell Therapy Kit SUI and the sterilization method (condition for sterility assurance level and residue of ethylene oxide sterilization) of the product. The data showed the conformity of product to the acceptance criteria defined.

5.B Outline of the review conducted by PMDA

PMDA reviewed the data on manufacturing process of Celution Cell Therapy Kit SUI and concluded that there was no particular problem.

6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare

The applicant submitted the results of the pivotal study of Celution Cell Therapy Kit SUI.

In addition, the applicant submitted an article on a feasibility study[5)] and a subsequent long-term clinical observation research[6)] as reference data.

6.A Summary of the data submitted

6.A.(1) Pivotal study (ADRESU Study)

A multicenter, open-label, uncontrolled study was conducted in patients with male SUI at 4 study sites in Japan to evaluate the efficacy and safety of periurethral injection of stromal stem cells.

The main inclusion and exclusion criteria are shown in Table 3. The pivotal study was conducted in a total of 43 patients with SUI persisting ≥1 year after prostate surgery who had no or inadequate response to behavioral or drug therapy, or were not eligible for drug therapy.

Table 3. Inclusion and exclusion criteria for the pivotal study

Inclusion criteria	1. Male patients with SUI persisting ≥1 year after surgery who have no or inadequate response[v] to behavioral and drug therapies, or are not eligible for drug therapy[vi] and meet the following criteria: (a) Patients with SUI developing after a radical prostatectomy (with negative resection margins of the isolated specimen) for localized prostate cancer (Gleason score, ≤7) that has not relapsed or metastasized for ≥1 year after surgery, with a PSA level of ≤0.1 ng/mL for ≥1 year after surgery (b) Patients with SUI developing after a transurethral prostatectomy or laser prostatectomy for prostatic hyperplasia, with a PSA level of ≤4.0 ng/mL for ≥1 year after surgery 2. Patients aged ≥20 years at the time of consent 3. Patients with the daily average amount of urine leakage of ≥30 and <300 g on a 24-hour pad test (mild to moderate) during the screening period
Exclusion criteria	1. Patients with urge incontinence, overflow incontinence, functional incontinence, or reflex incontinence, or those who have any of these types of urinary incontinence concomitantly 2. Patients who had a urinary or reproductive surgery involving resection within 6 months prior to consent 3. Patients who had a behavioral or drug therapy within 3 months prior to consent 4. Patients with concomitant diabetes insipidus 5. Patients with a history of local radiotherapy in the lower urinary tract 6. Patients with a history of treatment with stromal stem cells for SUI administered periurethrally 7. Patients who had any other cell therapy within 6 months prior to consent 8. Patients who participated or are participating in any other clinical study within 3 months prior to consent 9. Patients with concomitant lower urinary tract obstruction (e.g., prostatic hyperplasia) 10. Patients with concomitant urinary calculus (e.g., ureteric, urethral, or bladder calculus), urinary tract infection (e.g., prostatitis and cystitis), or interstitial cystitis

Table 4 shows the characteristics of patients enrolled in the pivotal study.

Table 4. Baseline characteristics of patients (FAS)

Characteristic		Celution group (N = 43)
Mean age (years)		70.3 ± 6.2
Mean body weight (kg)		66.43 ± 8.63
Surgical procedure causing SUI (n)	Radical prostatectomy for localized prostate cancer	39 (90.7%)
	Transurethral prostatectomy for prostatic hyperplasia	3 (7.0%)
	Laser prostatectomy for prostatic hyperplasia	1 (2.3%)

Age and body weight are expressed in mean ± SD

All 43 patients underwent the surgery under general anesthesia. Subcutaneous adipose tissue was collected only from the abdomen in [redacted] patients ([redacted]%), and the abdomen and buttocks in [redacted] patients ([redacted]%). The mean total volume of adipose tissue collected was [redacted] ± [redacted] mL.

The mean time required for stromal stem cell isolation was [redacted] ± [redacted] minutes. The mean volume of stem cell harvest isolated was [redacted] ± [redacted] mL. The mean [redacted] was [redacted] cells/[redacted] mL, and the mean [redacted] was [redacted]% ± [redacted]%. The mean time required for periurethral injection of stromal stem cells was [redacted] ± [redacted] minutes. In this study, the mean [redacted] was [redacted] ± [redacted] minutes.

6.A.(1).1) Efficacy evaluation

The primary efficacy endpoint was the "percentage of patients achieving a 50% reduction in urine leakage amount from baseline to Week 52 (hereinafter referred to as urine leakage responders)." The study results are shown in Table 5. The percentage of urine leakage responders was [redacted]%. With the lower limit of the 95% confidence interval of the percentage of responders exceeding the protocol-defined threshold of 10%, the primary endpoint was achieved.

[v] No sufficient improvement in urinary incontinence after approximately 3 months of behavioral therapy and drug therapy

[vi] Drug therapy is contraindicated, etc.

Table 5. Percentage of patients achieving a 50% reduction in urine leakage amount at Week 52 (FAS)

Time points		Overall patient population (N = 43)
Week 52/final evaluation point	n (%)	[redacted]
	95% CI	[redacted]

Missing data at Week 52 were imputed by the data from the final evaluation.
The 95% confidence interval was calculated by the Clopper-Pearson method.

Secondary efficacy endpoints were urine leakage amount based on various parameters and QOL (Tables 6 and 7). The QOL of patients was assessed using the International Consultation on Incontinence-Questionnaire-Short Form (ICIQ-SF) and the King's Health Questionnaire (KHQ), both of which are commonly used in QOL assessment in the treatment of urinary incontinence. A decrease in the ICIQ-SF or KHQ score indicates improvement. Patient satisfaction for treatment was assessed based on the VAS score. Among the secondary endpoints, the frequency of urinary incontinence and the number of bladder control pads used tended to improve more significantly over time. QOL assessment using the ICIQ-SF and KHQ suggested that the treatment with Celution Cell Therapy Kit SUI led to improvement in QOL.

Table 6. Results of secondary efficacy endpoints (other than KHQ)

	Baseline	Week [redacted]	Week [redacted]
Percentage of urine leakage responders (%)	-	[redacted]	[redacted]
Mean urine leakage amount (g) (N)	[redacted]	[redacted]	[redacted]
Percentage of urinary incontinence frequency responders (%)	-	[redacted]	[redacted]
Mean frequency of urinary incontinence (frequency) (N)	[redacted]	[redacted]	[redacted]
Mean number of bladder control pads used (number of pads) (N)	[redacted]	[redacted]	[redacted]
Mean ICIQ-SF score (N)	[redacted]	[redacted]	[redacted]
Mean patient satisfaction for treatment (N)	[redacted]	[redacted]	[redacted]
Mean maximum urethral closing pressure (cmH_2O) (N)	[redacted]	[redacted]	[redacted]
Mean functional profile length (mm) (N)	[redacted]	[redacted]	[redacted]
Mean abdominal leak point pressure (cmH_2O) (N)	[redacted]	[redacted]	[redacted]
Mean percentage of blood flow per sagittal sectional area (%) (N)	[redacted]	[redacted]	[redacted]
Mean adipose tissue volume (cm^3) (N)	[redacted]	[redacted]	[redacted]

Table 7. Results of the secondary endpoint of KHQ (mean ± SD)

	Baseline (N = [redacted])	Week [redacted] (N = [redacted])	Week [redacted] (N = [redacted])
General health perception	[redacted]	[redacted]	[redacted]
Incontinence impact	[redacted]	[redacted]	[redacted]
Role limitations	[redacted]	[redacted]	[redacted]
Physical limitations	[redacted]	[redacted]	[redacted]
Social limitations	[redacted]	[redacted]	[redacted]
Personal relationships	[redacted]	[redacted]	[redacted]
Emotions	[redacted]	[redacted]	[redacted]
Sleep/energy	[redacted]	[redacted]	[redacted]
Severity measures	[redacted]	[redacted]	[redacted]

6.A.(1).2) Safety evaluation

In the pivotal study, 8 severe adverse events occurred in 6 patients (13.3%). These events included wound complication and back pain in 2 patients (4.4%) each, and subcutaneous haematoma, haemoglobin decreased, bladder irritation, and embolism in 1 patient (2.2%) each. Of these events, embolism in 1 patient was assessed as serious. The event resolved after drug therapy with edoxaban tosilate hydrate and heparin sodium. A total of 11 moderate adverse events occurred in 8 patients (17.8%), including wound complication in 2 patients (4.4%), and inguinal hernia, pyrexia, bronchitis, pneumonia, ankle fracture, subcutaneous haematoma, blood creatine phosphokinase increased, c-reactive protein increased, and hypoxia in 1 patient (2.2%) each. Ankle fracture, inguinal hernia, and pneumonia in 1

patient each were assessed as serious. These events resolved or were resolving after intervention. A causal relationship to the stromal stem cells injected, the investigational device, or the procedure was ruled out for any of severe and moderate adverse events.

The pivotal study also revealed 2 adverse events for which a causal relationship to "a mixture of adipose tissue and stromal stem cells" or "stromal stem cells" could not be ruled out in 2 patients (4.4%). These events were dysuria in 1 patient (2.2%), which was assessed as probably related, and C-reactive protein increased in 1 patient (2.2%), which was assessed as possibly related. Both were mild in severity and resolved.

A total of 39 adverse events occurred in 36 patients (80.0%), for which a causal relationship to the study procedure could not be ruled out. Of these, 37 events in 35 patients (77.8%) were assessed as clearly related and 2 events in 2 patients (4.4%) were assessed as probably related. The adverse events assessed as clearly related included blood urine present in 34 patients (75.6%), and anaemia, haematuria, and urethral disorder in 1 patient (2.2%) each. The adverse events assessed as probably related included blood urine present and bladder spasm in 1 patient (2.2%) each.

No adverse event for which a causal relationship to the investigational device could not be ruled out was reported.

A total of 2 malfunctions occurred in 2 patients (4.4%). One of them was a breakage of a liposuction syringe, which did not lead to study discontinuation. The other was out-of-specification viability of stromal stem cells [see Section 2.(1)] that met the definition of malfunction according to the protocol. This malfunction was assessed as possibly related to the investigational device or study procedure and met the criteria for study discontinuation. Accordingly, the patient discontinued the study. No serious malfunction was reported.

6.A.(2) Clinical data submitted as reference data

The feasibility study was conducted to explore the possibility of treating male SUI by the use of the number of cells required that was estimated from the results of animal studies (Section 2.[8]). In this study, the change from baseline in daily mean urine leakage amount and the percent change at Month 12 were investigated in 11 patients. The mean change in leakage amount of [redacted] g and the mean percent change of [redacted]% suggested the efficacy of this treatment. A total of 13 patients including newly enrolled participants were followed in the subsequent long-term observation study. The daily mean urine leakage amount decreased from 260.7 g to 153.2 g at Month 60, with a percentage of urine leakage responders of 38.5% (5 of 13 patients). No particular adverse event was reported.

6.B Outline of the review conducted by PMDA

Taking account of the comments from the Expert Discussion, PMDA conducted reviews focusing on the following issues:

(1) Efficacy and safety

(2) Post-marketing safety measures

6.B.(1) Efficacy and safety

6.B.(1).1) Efficacy

The applicant's explanation:

In the pivotal study, the percentage of urine leakage responders at Week 52, the primary endpoint, was [redacted]% ([redacted] patients). Based on the lower limit of 95% confidence interval exceeding the threshold of 10%, the primary endpoint was achieved. Among the secondary endpoints, the frequency of urinary incontinence and the number of bladder control pads used tended to improve more significantly over time. QOL assessment using the ICIQ-SF suggested that the treatment with Celution Cell Therapy Kit SUI led to improvement in QOL. Of the KHQ domains, incontinence impact, role limitations, physical limitations, social limitations, personal relationships, emotions, sleep/energy, and severity measures tended to improve from baseline at each time point. These results indicate the efficacy of Celution Cell Therapy Kit SUI in the treatment of male SUI.

PMDA's view on the efficacy of Celution Cell Therapy Kit SUI:

SUI persisting for ≥1 year after prostate cancer surgery is said to be hardly likely to improve rapidly.[1)] [see Section 1.A.(1)]. For the percentage of urine leakage responders at Week 52, the primary efficacy endpoint, the protocol-defined threshold was 10%. Although this target was not high enough, the result was [redacted]% ([redacted] patients), indicating that Celution Cell Therapy Kit SUI has a certain level of efficacy of in the treatment of male SUI, for which there is no other treatment option, and satisfies an unmet medical need.

However, [redacted]% ([redacted] patients) of the non-responder population showed no reduction in urine leakage amount from baseline. PMDA asked the applicant to elaborate possible factors affecting the efficacy of Celution Cell Therapy Kit SUI.

The applicant's explanation:

The results of the primary endpoint in the pivotal study were reviewed in relation to the patient characteristics, the results of the secondary endpoints, and other possible factors such as study sites. The review identified no clear factors possibly related to the increased urine leakage amount. Nevertheless, the following factors are generally likely to be suggested as influential to the efficacy of Celution Cell Therapy Kit SUI and will be communicated to healthcare professionals. Patients who have poorly responded to the treatment with Celution Cell Therapy Kit SUI still remain eligible for the conventional surgical therapy, i.e., artificial urethral sphincter implantation.

- Patients with ongoing urethral stenosis prior to treatment (the transurethral endoscopic procedure dilates the urinary tract, which allows urethral stenosis to be relieved)
  - Patients with a large amount of residual urine, patients with urinary retention, and patients with symptoms of dysuria should be checked for urethral stenosis. Evident urethral stenosis should be treated before considering the treatment with Celution Cell Therapy Kit SUI. This information will also be communicated to healthcare professionals.
- Patients with urge incontinence, overflow incontinence, functional incontinence, or reflex incontinence
- Elderly patients (the urethral sphincter function may be impaired with aging)

PMDA's view:
Although no clear factors related to increased urine leakage was identified, the applicant's explanation is agreeable that generally patients with concomitant urethral stenosis or patients with urinary incontinence that is not associated with a prostate surgery (e.g., urinary bladder-related disease) are not be eligible for the treatment with Celution Cell Therapy Kit SUI. On the basis of the applicant's explanation, possible cautionary advice to be given to healthcare professionals at this stage and the principle for patient selection are understandable. Considering the current situation where there is no other treatment option, the clinical use of the product is acceptable. In addition, patients who have inadequate response to the treatment with the product will have the second option of artificial urethral sphincter implantation. Accordingly, the consideration of the use of Celution Cell Therapy Kit SUI is of clinical significance.

The details of post-marketing safety measures are described later.

6.B.(1).2) Safety

The applicant's explanation:
No adverse event related to Celution Cell Therapy Kit SUI was reported. Two adverse events for which a causal relationship to "a mixture of adipose tissue and stromal stem cells" or "stromal stem cells" could not be ruled out occurred in 2 patients (4.4%), and 39 adverse events for which a causal relationship to the study procedure could not be ruled out occurred in 36 patients (80.0%). All of the severe or moderate adverse events for which a causal relationship to the product could not be ruled out resolved or were resolving.

A serious embolism occurred in 1 patient. In this patient, extra time spent for liposuction consequently extended the entire surgical time and probably led to the deep vein thrombosis in legs. Therefore, a causal relationship to stromal stem cells, Celution Cell Therapy Kit SUI, or the study procedure[vii] was ruled out for the event. The patient recovered after drug therapy.

PMDA's view on the safety of Celution Cell Therapy Kit SUI:
All of the adverse events for which a causal relationship to Celution Cell Therapy Kit SUI could not be ruled out resolved or were resolving. Overall, the product has no safety issue. For the serious embolism reported, a direct causal relation to the product was ruled out, and the event did not affect the efficacy or safety of the product itself. However, the event is considered to have occurred due to the insufficient volume of adipose obtained by liposuction, an essential procedure for all patients undergoing the treatment, consequently prolonged the surgical time than expected. PMDA asked the applicant to explain any safety measures to prevent thrombosis from occurring.

The applicant's explanation:
The thrombosis was likely owing to the unexpectedly prolonged entire surgical time because of the prolonged liposuction. Healthcare professionals will be advised of the use of compression stockings or

[vii] Definition of the study procedure in the pivotal study: Every procedure from the start of using the investigational device through the injection of stromal stem cells or a mixture of adipose tissue and stromal stem cells

intermittent pneumatic compression (e.g., foot pump) during the adipose tissue harvest. According to literature research, the incidence of thromboembolism during liposuction was 0% to 0.18%,[7)-9)] which is not markedly higher than the incidence of pulmonary thromboembolism occurring in general surgery of 0.031%.[10)] No liposuction-specific risk factor for thrombosis has been identified. For these reasons, pre-operative risk assessment, preventive measures, post-operative tests, etc. according to the "Guidelines for Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis"[10)] will suffice for thrombosis control.

PMDA's view:
The applicant's explanation is reasonable. Appropriate preventive measures for thrombosis and embolism in the treatment should be taken with reference to the mentioned guidelines.

The submitted reference data from the 5-year observation following the feasibility study revealed no particular adverse event. However, these data were literature-based and of only a limited number of patients. Safety information should be collected through a use-results survey described later.

6.B.(2) Post-marketing safety measures

The applicant's explanation about measures to be taken to ensure proper use:
To ensure the safe use of Celution Cell Therapy Kit SUI, the following measures will be taken:

(a) Requirements for the use of Celution Cell Therapy Kit SUI
The guidelines for proper use will be developed in cooperation with academic societies concerned. The guidelines will specify requirements for surgeons and other requirements to ensure appropriate use of the product and the safety of procedure that is performed by surgeons with adequate knowledge and experience in treating and diagnosing male lower urinary tract symptoms who fully understand the efficacy and safety of the product. The guidelines will also advise appropriate cooperation with the plastic surgery department. To allow for appropriate information provision to patients at any medical institutions providing the treatment, a template of consent form will be attached in the guidelines.

(b) Training
Educational training will be provided to surgeons who will handle Celution Cell Therapy Kit SUI.

PMDA's view on the post-marketing safety measures for Celution Cell Therapy Kit SUI:
The treatment with Celution Cell Therapy Kit SUI is unique from the conventional treatments in Japan. The treatment involves not only an endoscopic operation but also accurate adipose tissue collection from the abdomen or other sites that needs support from the plastic surgery specialists, etc. and a series of subsequent procedures including isolation and injection that need to be performed in a prompt manner. The treatment also requires an accurate injection technique, i.e., the injection of a total of 1 mL of stromal stem cells into the right and left sides of the external urethral sphincter, followed by the submucosal injection of a 20-mL mixture of adipose tissue (16 mL) and stromal stem cells (4 mL) into the right and left sides of the membranous urethra. Furthermore, patients to be treated must be selected appropriately based on the inclusion/exclusion criteria used in the clinical study and the results of the clinical study.

In summary, the applicant should cooperate with academic societies concerned in formulating the guidelines for proper use that will contain patient selection criteria and requirements for surgeons and medical institutions. Furthermore, the applicant should also hold post-marketing training, etc. for healthcare professionals to familiarize them with the proper use of the product. To facilitate their adherence to the guidelines for the use, approval conditions should be attached.

7. Plan for Post-marketing Surveillance etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the data submitted

Because efficacy and safety data of Celution Cell Therapy Kit SUI in Japanese patients need to be collected from clinical settings, PMDA instructed the applicant to plan a survey with a specific period, sample size, survey items, etc. The applicant submitted a draft use-results survey plan (Table 8).

Table 8. Use-results survey plan submitted by the applicant (draft)

Objectives	The verification of the safety and efficacy of Celution Cell Therapy Kit SUI in clinical use in patients treated with the product
Survey population	Male SUI
Sample size (planned)	Planned sample size, all patients (≥120 patients)
Planned survey period	5 years from the approval date (preparation, 6 months; enrollment, 36 months; follow-up, 12 months; and analysis, 6 months)
Summary of survey methodology	Data of the items listed below will be collected during the follow-up period (Months 1, 3, 6, and 12). A use-results survey report will provide safety and efficacy analyses and evaluation based on the data collected.
Main survey/evaluation items	Sex and age, medical history and complications, causative surgery of SUI, 24-hour urine leakage, frequency of urine incontinence in 24 hours, ICIQ-SF, the number of bladder control pads used daily, uroflowmetry (maximum urine flow and urine output), residual urine volume, pre-operative urethral stenosis, adverse events, blood test, and urinalysis

Rationale for the sample size:

Because Celution Cell Therapy Kit SUI is used for a novel therapy, a use-results survey should include all patients who receive the treatment. Approximately 60 patients (6 sites and approximately 10 patients per site) per year are expected to be treated with the product after its introduction to clinical practice. The minimum sample size of 120 was determined based on the estimation that 120 patients would undergo the procedure during the 3-year enrollment period. In the pivotal study, adverse events for which a causal relationship to “a mixture of adipose tissue and stromal stem cells” or “stromal stem cells” could not be ruled out occurred in 2 of 45 patients (4.4%). A use-results survey involving ≥120 patients has power to detect ≥1 adverse event or malfunction with an incidence of ≥2.5% with a probability of ≥95%. The pivotal study revealed serious adverse events in 6 of 45 patients (13.3%) and device malfunctions in 2 of 45 patients (4.4%). The sample size is large enough to detect serious adverse events and device malfunctions.

7.B Outline of the review conducted by PMDA

PMDA’s view:

The draft use-results survey plan submitted by the applicant is acceptable.

However, the use-results survey will provide only limited information about long-term prognosis. The guidelines for proper use need to be formulated so that long-term prognosis-related information is collected through academic societies concerned. The applicant also needs to cooperate with the

academic societies concerned in taking risk mitigation measures as necessary based on long-term prognosis-related information that will be available from the post-marketing setting.

III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

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

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

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

The new medical device application data 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.

IV. Overall Evaluation

Celution Cell Therapy Kit SUI is a single-use kit consisting of an adipose tissue collection container, a processing chamber, a waste bag, a tubing set, and an enzyme (Celase). The product is used in combination with a centrifuge to isolate stromal stem cells from adipose tissue collected from the patient. Isolated stromal stem cells are used in the treatment of male SUI. The main issues in the regulatory reviews of the product were (1) clinical positioning, (2) efficacy and safety, (3) post-marketing safety measures, and (4) use-results survey.

PMDA's conclusions based on comments from the Expert Discussion:

(1) Clinical positioning

Celution Cell Therapy Kit SUI is indicated for the treatment of SUI, a complication secondary to a surgery for prostatic hyperplasia or prostate cancer. However, the "Clinical Guidelines for Male Lower Urinary Tract Symptoms and Benign Prostatic Hyperplasia"[11] has no section describing SUI. The "Guidelines for Urinary Incontinence in Elderly People (in Japanese)"[12] currently recommend behavioral, drug, or surgical therapy to treat SUI. However, a certain number of patients with SUI developing as a post-surgical complication do not respond to behavioral or drug therapy and have persistent symptoms for ≥1 year after surgery. To manage severe symptoms in patients with such refractory SUI, an artificial urethral sphincter is used. In contrast, patients with mild or moderate symptoms do not have other therapeutic options unless using an artificial urethral sphincter.

Based on the above, Celution Cell Therapy Kit SUI should be used to treat SUI which is not severe enough to consider artificial urethral sphincter implantation but are inadequately responding to or are contraindicated to other therapies. The product is a clinically significant medical device that satisfies the unmet medical need. Meanwhile, SUI may be caused by neurogenic bladder associated with spina bifida

or traumatic injury. The use of the product, however, should be limited to the treatment of SUI secondary to a surgery for prostatic hyperplasia or prostate cancer as specified in the inclusion criteria of the pivotal study.

(2) Efficacy and safety

In the pivotal study, the percentage of urine leakage responders at Week 52 was [redacted]%, achieving the primary endpoint. Possible causes of increased urine leakage observed in the study will be mentioned in precautions and other information and in the guidelines for proper use to be communicated appropriately to healthcare professionals. In response to the occurrence of thromboembolism in 1 patient (2.2%) during liposuction, advice will be given in precautions and other information as well as in the guidelines for proper use that thromboembolism be treated by a standard of care in accordance with the "Guidelines for Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis."[10)]

An article on the feasibility study[5)] and the subsequent long-term clinical observation study[6)] submitted as reference data presented no particular efficacy or safety problem at 5 years postoperative.

On the basis of a comprehensive review, the benefits of Celution Cell Therapy Kit SUI overweigh its risk. The efficacy and safety evaluation data is acceptable.

(3) Post-marketing safety measures

In Japan, there is no product or procedure similar to Celution Cell Therapy Kit SUI. As mentioned, the surgeon must accurately inject stromal stem cells and a mixture of stromal stem cells and adipose tissue at the right spots. The treatment requires appropriate patient selection as well as peri- and post-operative measures against adverse events.

Accordingly, post-marketing safety measures need to be taken in close cooperation with academic societies concerned for the formulation of the guidelines for proper use that contain patient selection criteria and requirements for surgeons and medical facilities, and further in offering training opportunities in the post-marketing setting to ensure the proper use of Celution Cell Therapy Kit SUI. To facilitate healthcare professionals' adherence to the guidelines, approval conditions should be attached.

(4) Use-results survey

Because of no similar types of conventional medical devices or procedures in Japan, the treatment with Celution Cell Therapy Kit SUI has hardly been established in the country.

To understand the usage of Celution Cell Therapy Kit SUI for a certain period of time in the post-marketing setting and to verify the product's efficacy and safety, a use-result survey should be implemented for 5 years (preparation, 6 months; registration, 36 months; follow-up, 12 months; and analysis, 6 months).

On the basis of the above discussions, PMDA concludes that Celution Cell Therapy Kit SUI may be approved for the intended use modified as shown below, with the following conditions.

Intended Use

Celution Cell Therapy Kit SUI is a single-use special kit to separate, clean, and process adipose tissue by centrifugation to obtain specific cells or tissue to be administered to patients with mild to moderate stress urinary incontinence associated with urethral sphincter incompetence secondary to a surgery for prostatic hyperplasia or prostate cancer who have no or inadequate response to behavioral and drug therapies.

Approval Conditions

1. The product should be used by surgeons with adequate knowledge and experience in the treatment of male lower urinary tract symptoms who have acquired competent skills for the use of the product and knowledge about procedure-associated complications, and at medical institutions with a well-organized care system. To fulfill these requirements, the applicant is required to take any necessary measures in cooperation with academic societies concerned.
2. The applicant is required to disseminate the guidelines for proper use developed by academic societies concerned, hold seminars, and take other necessary measures.
3. The applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, submit the results of interannual analyses to the Pharmaceuticals and Medical Devices Agency, and take other appropriate measures as necessary.

The product is not classified as a biological product or a specified biological product. The product is designated as a medical device subject to a use-results survey. The use-results survey period should be 5 years.

PMDA concludes that this application should be subject to deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

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12) Guidelines for Urinary Incontinence in Elderly People (in Japanese) (Project for Comprehensive Research on Aging and Health founded by the 2000 Health and Labour Sciences Research Grants)

Review Report (2)

November 18, 2021
Pharmaceuticals and Medical Devices Agency

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

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Adipose tissue separation kit
Brand Name	Celution Cell Therapy Kit SUI
Applicant	Cytori Therapeutics, K.K.
Date of Application	December 24, 2019
Reviewing Office	Office of Medical Devices II

Review Results

November 18, 2021

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Adipose tissue separation kit
Brand Name	Celution Cell Therapy Kit SUI
Applicant	Cytori Therapeutics, K.K.
Date of Application	December 24, 2019

Results of Review

On the basis of the conclusions by Pharmaceuticals and Medical Devices Agency (PMDA) in the Review Report dated August 6, 2021 (Review Report [1]), the approval application for Celution Cell Therapy Kit SUI was subjected to deliberation at the meeting of the Committee on Medical Devices and *In-vitro* Diagnostics on September 1, 2021. At this meeting, the committee made remarks on the clinical significance of the use of stromal stem cells and the justification for the single-arm design of the pivotal study. Thus the meeting concluded that the deliberation should be continued to further discuss the efficacy of the product based on additional basic research data on stromal stem cell therapy and clinical information, etc. that complement the clinical study results.

The clinical significance of the use of stromal stem cells: In the past, stress urinary incontinence (SUI) had been treated with bovine collagen, an approved injectable for intraurethral therapy, in Japan. Bovine collagen, however, is no longer available in Japan or overseas because of the problem with bovine spongiform encephalopathy (BSE), etc. The transplantation of autologous adipose tissue collected from patients themselves to replace their fragile or lost tissue has already been introduced to multiple medical fields. However, long-term engraftment and stability were challenging issues of tissue transplantation due to early absorption, the nature of adipose tissue. These challenges led to the development of the therapeutic method for male SUI in Japan. The new method uses not adipose tissue alone but a mixture of adipose tissue and stromal stem cells to allow for long-term tissue engraftment. Making use of the approved kit for stromal stem cell separation, the application for marketing approval for Celution Cell Therapy Kit SUI was submitted for the additional indication of male SUI.

The justification for the single-arm design of the pivotal study: The pivotal study submitted was conducted in an open-label design because (a) there is no other therapy that has been proven as best control; (2) a sham procedure, if used as control, would also require patients to undergo adipose tissue collection only for blinding purpose. The tissue collection does not contribute to the treatment and rather poses an unnecessary additional risk for patients in the control group, which is ethically unacceptable; and (3) the use of a treatment-naive group would be difficult because of the known fact that SUI persisting for ≥1 year after prostate surgery is less likely to improve spontaneously. The results of the pivotal study are not markedly

inferior to the injection therapy with the approved collagen, the product withdrawn from the market in Japan and overseas.

As a result of its review, PMDA has considered that Celution Cell Therapy Kit SUI may be approved for the intended use shown below, with the following conditions because the product is clinically useful in intraurethral injection therapy to treat male SUI in Japan, and that the application should be subjected to deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

Intended Use

Celution Cell Therapy Kit SUI is a single-use special kit to separate, clean, and process adipose tissue by centrifugation to obtain specific cells or tissue to be administered to patients with mild to moderate stress urinary incontinence associated with urethral sphincter incompetence secondary to a surgery for prostatic hyperplasia or prostate cancer who have no or inadequate response to behavioral and drug therapies.

Approval Conditions

1. The product should be used by surgeons with adequate knowledge and experience in the treatment of male lower urinary tract symptoms who have acquired competent skills for the use of the product and knowledge about procedure-associated complications, and at medical institutions with a well-organized care system. To fulfill these requirements, the applicant is required to take any necessary measures in cooperation with academic societies concerned.
2. The applicant is required to disseminate the guidelines for proper use developed by academic societies concerned, hold seminars, and take other necessary measures.
3. The applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, submit the results of interannual analyses to the Pharmaceuticals and Medical Devices Agency, and take other appropriate measures as necessary.

Review Report

November 18, 2021

Product for Review

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Adipose tissue separation kit
Brand Name	Celution Cell Therapy Kit SUI
Applicant	Cytori Therapeutics, K.K.
Date of Application	December 24, 2019
Proposed Intended Use	Celution Cell Therapy Kit SUI is a single-use special kit to separate, clean, and process adipose tissues by centrifugation to obtain specific cells or tissue for the treatment of patients with male stress urinary incontinence.

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List of Abbreviations

BSE	Bovine Spongiform Encephalopathy
MRI	Magnetic Resonance Imaging
QOL	Quality of Life
SUI	Stress Urinary Incontinence

I. Content of the Review

On the basis of the conclusions by Pharmaceuticals and Medical Devices Agency (PMDA) in the Review Report (Review Report "Celution Cell Therapy Kit SUI" dated August 6, 2021, Review Report [1]), the application for Celution Cell Therapy Kit SUI was subjected to deliberation at the meeting of the Committee on Medical Devices and *In-vitro* Diagnostics on September 1, 2021. At the meeting, the committee made remarks about the clinical significance of the use of stromal stem cells and the justification for the single-arm design of the pivotal study. The committee requested the applicant to submit basic research data on stromal stem cell therapy and clinical information, etc. other than the clinical study results for further discussion on the efficacy of the product. The deliberation should thus be continued.

The following summarizes the review at PMDA for continuous deliberation.

(1) Clinical positioning of Celution Cell Therapy Kit SUI in Japan and overseas

1) Current injection therapy for the treatment of male stress urinary incontinence

Stress urinary incontinence (SUI) refers to an involuntary leakage of urine occurring without bladder contractions during moments of physical activity that increases abdominal pressure, such as exertion/exercising, coughing, sneezing. In men, it may occur as a complication of a surgery fort prostatic hyperplasia or prostate cancer. In Japan, the "Guidelines for Urinary Incontinence in Elderly People (in Japanese)"[1)] and the "Clinical Guidelines for Female Lower Urinary Tract Symptoms"[2)] have been developed. Both guidelines provide in-depth discussions on female urinary incontinence but mention male urinary incontinence only briefly. In addition, the "Clinical Guidelines for Male Lower Urinary Tract Symptoms and Benign Prostatic Hyperplasia"[3)] have no section describing male SUI. The current major first-line treatment options for male SUI in Japan are behavioral and drug therapies. For patients who do not respond to either therapy, surgical therapy is selected.

The US guidelines[4)] and the European guidelines[5)] introduce "artificial urethral sphincter implantation," "male sling surgery," "ProAct device," or "intraurethral injection therapy" as a surgical therapy for male SUI. In the US, 3 types of injectables are available for "intraurethral injection therapy," namely, "Durasphere" (pyrolytic carbon-coated zirconium oxide spheres), "Coaptite" (spherical particles of calcium hydroxylapatite), and "Macroplastique" (polydimethylsiloxane) (all not approved in Japan). For being artificial materials, these injectables are more likely to cause xenobiotic reaction-induced adverse events at the implantation site as compared with autologous tissue.

While these therapies are available in the US, "artificial urethral sphincter implantation" and "intraurethral injection therapy" using bovine collagen (approved product in Japan "Bard Contigen," Approval number 20600BZY01080000) (collagen injection surgery to treat urinary incontinence or vesicoureteral reflux) are the only surgical options for male SUI covered by insurance in Japan. "Bard Contigen" was however withdrawn from Japanese and overseas markets around 2009 because of the problem with bovine spongiform encephalopathy (BSE), etc. associated with bovine-derived raw materials. Thus, in Japan, no intraurethral injectable is available, and highly invasive artificial urethral sphincter implantation is currently the only surgical option for male SUI.[2)]

The use of injectable autologous adipose tissue or physiological saline have been reported through clinical researches. According to the literature on non-Japanese female SUI, the urinary incontinence improvement rate at 3 months after injection was 20s% (22.2% in the adipose group and 20.7% in the physiological saline group).[6] The literature reported that injectable autologous adipose tissue or physiological saline needed to be injected at least once monthly and the therapeutic effect of a single injection of either injectable can last only 1 month or so.

In this situation in Japan, there has been a demand for a new injectable with a certain long-lasting therapeutic effect and less risk of complications caused by its xenobiotic reaction.[7]

2) Treatment with Celution Cell Therapy Kit SUI not approved overseas

As explained in 1) above, there are multiple therapeutic options for male SUI overseas as compared with Japan because (a) ≥1 intraurethral injectables, other than bovine collagen, are approved and sold, and (b) ≥1 other surgical procedures are available overseas. The applicant thus decided to apply for a marketing approval of Celution Cell Therapy Kit SUI first in Japan, in view of the current unmet medical need in the country and the much greater demand for the clinical use of the product in Japan than in other countries .

As described in the Review Report (1), Celution devices have widely been used in overseas clinical settings for reconstruction after mastectomy or prosthetic surgery to repair anatomical soft tissue defects. In Japan, Celution Cell Therapy Kit has been approved for the intended use described as "Celution Cell Therapy Kit is a special kit to separate, clean, and process adipose tissues by centrifugation to obtain specific cells or tissue to be administered. Celution Cell Therapy Kit is single use." (Approval number 23000BZX00357000, hereinafter referred to as "the applicant's approved product") prior to Celution Cell Therapy Kit SUI.

As explained in 1) and 2) above, the product was developed to obtain autologous adipose tissue and stromal stem cells for the injectable mixture, as an alternative to bovine collagen that is no longer available in Japan, for intraurethral injection therapy to treat male SUI. The basic information about the product and cells obtained by the product is provided via existing clinical information including breast reconstruction implemented overseas and the data of the applicant's approved product attached to the previous application.

(2) Additional discussion on the efficacy of Celution Cell Therapy Kit SUI

Supplementary information on the efficacy evaluation of Celution Cell Therapy Kit SUI reported in the Review Report (1) is presented below.

1) Clinical information on stromal stem cells other than basic research and the results of the clinical study

The transplantation of autologous adipose tissue has been applied to the treatment of vocal cord paralysis, facial reconstruction, or mammoplasty. However, the absorption of transplanted adipose tissue remained an issue. Meanwhile, basic researches[8),9)] and clinical researches began to suggest that the use of a mixture of stromal stem cells and adipose tissue helps prolong adipose tissue engraftment. For example, according to a report on breast reconstruction in humans, the transplantation of a mixture of adipose tissue and stromal stem cells succeeded to maintain the breast thickness significantly at Month 6 as compared with the transplantation of adipose tissue alone.[10)]

The above finding motivated the applicant to consider the use of a mixture of autologous adipose tissue and stromal stem cells in the intraurethral injection therapy.

As described in the Review Report (1), a nonclinical study on leak point pressure after the periurethral injection of stromal stem cells demonstrated the therapeutic effect of periurethral injection of stromal stem cells in SUI model rats. This study showed that the injection of [redacted] cells induced [redacted] of [redacted], and [redacted] significantly improved [redacted] relative to [redacted]. The data also suggested that improvement in [redacted] led to [redacted].

Based on the above basic research and clinical information, the applicant, with the expectation that stromal stem cells would have an effect to improve long-term tissue engraftment, which would take the place of bovine collagen, decided to start a clinical study for the application of Celution Cell Therapy Kit SUI to intraurethral injection therapy to treat male SUI. Albeit its evidence level not high enough, 1 case of male SUI treated with stromal stem cells has been reported in Korea.[11)]

2) Results of the pivotal study of Celution Cell Therapy Kit SUI

(a) Summary of the pivotal study

Based on the efficacy of the treatment suggested in the feasibility study, the applicant planned a pivotal study. The pivotal study was conducted at 4 study sites in Japan with a multicenter, open-label, uncontrolled design to evaluate the efficacy and safety of the product in the treatment of male SUI. The pivotal study enrolled 43 patients with SUI persisting ≥1 year after prostate surgery who had no or an inadequate response to behavioral or drug therapy, or were ineligible for drug therapy. The primary efficacy endpoint was the "percentage of patients achieving a 50% reduction in urine leakage amount from baseline to Week 52 (urine leakage responders)." The percentage of urine leakage responders was [redacted]% ([redacted] patients). With the lower limit of the 95% confidence interval of the percentage of responders exceeding the protocol-defined threshold of 10%, the primary endpoint was achieved.

The secondary endpoints included the urine leakage amount, frequency of urinary incontinence, the number of bladder control pads used, quality of life (QOL), and patient satisfaction for treatment. As shown in the Review Report (1), these endpoints tended to improve during the study.

Table 1 shows a comparison of urine leakage amount between the responder group and the non-responder group. The responder group achieved the mean improvement in urine leakage amount of [redacted]%.

Table 1. Comparison of urine leakage amount and improvement rate at Week 52 between responders and non-responders

	Baseline urine leakage amount	Urine leakage amount at Week 52	Improvement rate
Responder (N = [redacted])	[redacted] ± [redacted] g	[redacted] ± [redacted] g	[redacted] ± [redacted] g
Non-responder (N = [redacted])	[redacted] ± [redacted] g	[redacted] ± [redacted] g	[redacted] ± [redacted] g

The mean decrease in the number of bladder control pads used was approximately 1, not a substantial decrease. However, because the decision on when to change bladder control pads depended on individual patients, there is no clear correlation between the number of pads used and the urine leakage amount.

Nevertheless, the QOL scores and patient satisfaction tended to improve, indicating the clinical significance of the treatment.

In the feasibility study conducted prior to the pivotal study to explore the possibility of treating male SUI, change from baseline in daily mean urine leakage amount and the percent change at Month 12 were investigated in 11 patients. The mean change was [redacted] g with the mean percent change of [redacted]%, suggesting the efficacy of this treatment.

No serious adverse event related to Celution Cell Therapy Kit SUI or the injectables was reported in either pivotal or feasibility study.

(b) Engraftment of adipose tissue injected

The magnetic resonance imaging (MRI) in the pivotal study confirmed that the adipose tissue injected maintained its conformational structure (Figure 1).

Figure 1. MRI images after injection of a mixture of adipose tissue and stromal stem cells
[redacted]

Following the feasibility study prior to the pivotal study, 13 patients underwent a long-term observation. The daily mean urine leakage amount decreased from 260.7 g at baseline to 153.2 g at Month 60, and the percentage of urine leakage responders was 38.5% (5 of 13 patients).[12)]

These results indicate the long-term efficacy of the treatment with Celution Cell Therapy Kit SUI.

3) Justification for the design of the pivotal study on Celution Cell Therapy Kit SUI

The pivotal study employed a single-arm design, and its justification and reasons are explained below.

- In the situation where injectable bovine collagen has been withdrawn from the Japanese market, the treatment with Celution Cell Therapy Kit SUI can be considered as an unmet medical need. Physiological saline and autologous adipose tissue, candidate control substances, have not been used in clinical practice because of their poor therapeutic effect and low retention, and are neither proven as best treatment nor appropriate to be used as control substances.

- The use of a sham procedure with no injection is also unsuitable as control in this pivotal study. Patients assigned to the sham group will still need to undergo liposuction for a blinding purpose. This procedure unrelated to the control treatment can pose additional risks to these patients.
- The use of a treatment-naive control group is less than meaningful. The product is intended for patients with SUI persisting for ≥1 year after a prostate surgery, and their symptoms are known to remain unimproved unless treated. Because SUI is caused by mechanical damage of the sphincter, urinary incontinence can hardly be controlled voluntarily. The therapeutic effect on urinary incontinence is evaluable appropriately in the absence of a treatment-naive control group.

On the basis of the above comprehensive discussions, the single-arm design was selected for the pivotal study of Celution Cell Therapy Kit SUI.

4) Outcome of collagen injection

As mentioned, periurethral collagen injection used to be practiced in the treatment of Japanese male SUI but is no longer available in the domestic market. Injectable collagen is absorbed in the body in several weeks after injection, resulting in the recurrence of urinary incontinence in 1 to 3 months. Collagen injection therapy is thus known to have less long-lasting effect. The following have been reported about the outcomes of collagen injection in the treatment of male SUI after a prostate surgery.

- A total of 20 patients received 5 to 25 mL (mean, 14.5 mL) of collagen. Subjective cure was observed in 25% of the patients, improvement in 45%, and no improvement in 30% (mean follow-up period, 9.5 months).[13] Note that collagen was injected endoscopically to a vesical fistula created in the lower abdomen, not transurethrally.
- A total of 67 patients received 8 to 125 mL (mean, 36 mL) of collagen. Cure (no need for bladder control pads or urinary continence) was achieved in 10% of the patients, high improvement in 10%, slight or no improvement in 67%, and aggravation in 13%. The frequency of injections ranged from 3 to 15 (mean, 5). The follow-up period continued for 6 to 46 months (mean, 38 months).[14]
- A total of 19 patients received 16 mL (mean) of collagen. At Month 3, all patients returned to the baseline urinary continence state.[15]
- A total of 19 patients received 3 to 32.5 mL of collagen. The treatment was successful (urinary continence or occasional use of bladder control pads) in 4 patients, improved (75% decrease) in 7 patients, and failed in 8 patients. The frequency of injections ranged from 1 to 3. The follow-up period lasted for 3 to 15 months.[16]

(3) Stromal cell yield of Celution Cell Therapy Kit SUI (based on the approved product)

The following describes basic performance and specifications of stromal stem cells used in this treatment based on the approved basic information of the applicant's approved product.

The treatment requires the aspiration of 250 to 300 mL subcutaneous adipose tissue, from which stromal stem cells are isolated. When Celution Cell Therapy Kit SUI was used according to the standard procedure for cell isolation, [redacted] ± [redacted] mL of cells was yielded in the chamber, with [redacted] of [redacted]% ± [redacted]%, [redacted] of [redacted] ± [redacted] cells/g, and [redacted] of [redacted]% ± [redacted]%.

(4) Contents of the guidelines for proper use to be developed by academic societies concerned

Prior to the approval for Celution Cell Therapy Kit SUI, requirements for surgeons and medical institutions will be specified in the guidelines for proper use. To ensure that all medical institutions involved provide patients with appropriate information, the template of informed consent will be attached to the guidelines. The template should provide careful description of the product characteristics, including the summary results of the pivotal study, to help patients understand the treatment correctly and enable doctors to confirm appropriately whether the patient wishes to receive the treatment.

II. Overall Evaluation

Celution Cell Therapy Kit SUI is a single-use kit to be used in combination with a centrifuge to isolate stromal stem cells from adipose tissue collected from the patient. Isolated stromal stem cells are used to treat male SUI. At a meeting on September 1, 2021, the Committee on Medical Devices and *In-vitro* Diagnostics made remarks on supplementary basic information about the therapeutic effect of treatment with the product and the interpretation of the study results in Japan. In response, PMDA further reviewed information about the approved product and literature on the treatment or relevant matters, and came to the following conclusions, in addition to those reached in the Review Report (1):

(1) Justification for the use of Celution Cell Therapy Kit SUI in the treatment of male SUI in Japan

As described in I, the results of the pivotal study yielded results of treatment with Celution Cell Therapy Kit SUI that was not particularly inferior to the clinical results of collagen injection therapy, although not by a direct comparison. Considering that injectable collagen is no longer available in Japan, the product is a clinically significant medical device that satisfies the unmet medical need. The treatment with autologous tissue involves no artificial materials and thus raises no raw material-related safety concerns. For these reasons, Celution Cell Therapy Kit SUI is considered to have a better risk-benefit balance as compared to the approved collagen injection therapy. The pivotal study was designed with a single treatment arm, which is acceptable in light of the difficulty specifying a control group, as explained in I.

In conclusion, the efficacy and safety of Celution Cell Therapy Kit SUI can be evaluated based on the results of the pivotal study. It is reasonable to use the product in the treatment of male SUI in Japan.

(2) Proper use of Celution Cell Therapy Kit SUI in the post-marketing setting

The guidelines for proper use of Celution Cell Therapy Kit SUI will be formulated in cooperation with academic societies concerned. Whether the patient wishes to receive the treatment with the product will be confirmed via the template of consent form attached to the guidelines that helps them understand the treatment correctly. As described in the Review Report (1), a use-results survey will be conducted in all patients who receive the treatment in the post-marketing setting. In conclusion, PMDA considers that the post-marketing measures for the proper use of the product are reasonable.

On the basis of its review, PMDA has concluded that Celution Cell Therapy Kit SUI may be approved after modifying the intended use as shown below, with the following approval conditions.

Intended Use

Celution Cell Therapy Kit SUI is a single-use special kit to separate, clean, and process adipose tissue by centrifugation to obtain specific cells or tissue to be administered to patients with mild to moderate stress urinary incontinence associated with urethral sphincter incompetence secondary to a surgery for prostatic hyperplasia or prostate cancer who have no or inadequate response to behavioral and drug therapies.

Approval Conditions

1. The product should be used by surgeons with adequate knowledge and experience in the treatment of male lower urinary tract symptoms who have acquired competent skills for the use of the product and knowledge about procedure-associated complications, and at medical institutions with a well-organized care system. To fulfill these requirements, the applicant is required to take any necessary measures in cooperation with academic societies concerned.
2. The applicant is required to disseminate the guidelines for proper use developed by academic societies concerned, hold seminars, and take other necessary measures.
3. The applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, submit the results of interannual analyses to the Pharmaceuticals and Medical Devices Agency, and take other appropriate measures as necessary.

The product is not classified as a biological product or a specified biological product. The product is designated as a medical device subject to a use-results survey. The use-results survey period should be 5 years.

This application should be subjected to deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

References

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