

January 15, 2016

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

Report on the Deliberation Results

Category	Instrument & Apparatus 72, Lens for Vision Correction
Term Name	Limbal-supported contact lens for abnormal corneal shape
Brand Name	Suncon Kyoto-CS
Applicant	Sun Contact Lens Co., Ltd.
Date of Application	June 30, 2015 (Application for marketing approval)

Results of Deliberation

The results of deliberation of the Committee on Medical Devices and *In-vitro* Diagnostics on January 15, 2016, are as described below. The committee concluded that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product should be designated as a medical device subject to the use-results survey and approved with the following condition. The product is classified as a specially controlled medical device and is not classified as a specially designated maintenance-and-management-required medical device. The product is not classified as a biological product or a specified biological product.

Condition of Approval of the Marketing Application

The applicant is required to cooperate with related academic societies and take necessary actions to ensure the proper use of the product. For instance, knowledge and skills training may be provided to prescribing physicians, who must have established knowledge and experience in treating conditions relevant to the indication for the product, so as to enhance their prescription skills.

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

December 16, 2015

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).

Category	Instrument & Apparatus 72, Lens for Vision Correction
Term Name	Limbal-supported contact lens for abnormal corneal shape (to be newly named)
Brand Name	Suncon Kyoto-CS
Applicant	Sun Contact Lens Co., Ltd.
Date of Application	June 30, 2015
Items Warranting Special Mention	Orphan medical device
Reviewing Office	Office of Medical Devices III

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Review Results

December 16, 2015

Category	Instrument & Apparatus 72, Lens for Vision Correction
Term Name	Limbal-supported contact lens for abnormal corneal shape (to be newly named)
Brand Name	Suncon Kyoto-CS
Applicant	Sun Contact Lens Co., Ltd.
Date of Application	June 30, 2015

Results of Review

Suncon Kyoto-CS is a limbal-supported, rigid contact lens for patients with ocular sequelae of Stevens Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) to alleviate symptoms associated with severe dry eye, etc. and to correct visual acuity.

The applicant submitted the non-clinical data related to the physiochemical characteristics, biological safety, stability and durability, and performance of Suncon Kyoto-CS. PMDA identified no particular problem with these properties.

The applicant submitted the clinical data from an investigator-initiated clinical study in Japan (hereinafter referred to as “the clinical study”). The clinical study is a prospective, multicenter, single-arm study in 10 patients with an ocular sequela of SJS or TEN conducted to evaluate the safety and clinical efficacy of Suncon Kyoto-CS.

The primary endpoint of the clinical study was improvement in best corrected visual acuity (BCVA) with the investigational contact lens, and the 10 patients were evaluated for BCVA. The improvement rate reached 80.0%, exceeding the threshold for protocol-specified clinically significant improvement of 50.0%. Safety evaluation was performed on the 10 patients. Adverse events with a suspected causal relationship to the device were conjunctival erosion and eye discharge. The former occurred in 2 patients (3 cases) and was causally related to the device, while the latter occurring in 1 patient (1 case) had an unknown causality. All these events were mild in severity. There was no serious adverse event.

The submitted data are satisfactory relevant to evaluate the efficacy and safety of Suncon Kyoto-CS. PMDA reviewed the data comprehensively based on the discussions at the Expert Discussion. Considering the lack of therapeutic options in Japan for visual acuity correction and the alleviation of symptoms in patients with an ocular sequela of SJS or TEN, it is of significance to make this an orphan medical device available in clinical practice. To ensure the safety and efficacy of Suncon Kyoto-CS,

appropriate assessment of patient eligibility and accurate fitting, etc. are important. Therefore, treating physicians must have relevant knowledge and experience to prescribe the device as intended, with a good understanding of its characteristics, and this should be mentioned as a condition of the approval of the product.

As a result of its review, PMDA has concluded that Suncon Kyoto-CS may be approved for the following intended use with the condition below, and that the application should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use

Correction of visual acuity and alleviation of symptoms in patients with an ocular sequela of Stevens Johnson syndrome or toxic epidermal necrolysis who do not achieve satisfactory visual acuity using conventional eye glasses and contact lenses.

Condition of Approval

The applicant is required to cooperate with related academic societies and take necessary actions to ensure the proper use of the product. For instance, knowledge and skills training may be provided to prescribing physicians, who must have established knowledge and experience in treating conditions relevant to the indication for the product, so as to enhance their prescription skills.

Review Report

December 16, 2015

I. Product Submitted for Approval

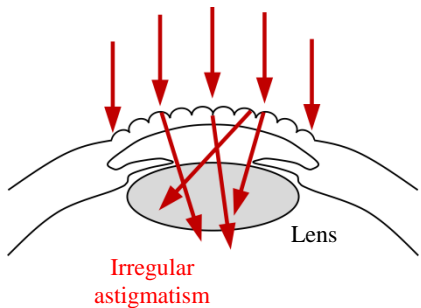
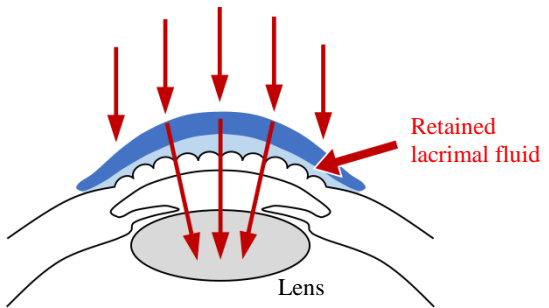
Category	Instrument & Apparatus 72, Lens for Vision Correction
Term Name	Limbal-supported contact lens for abnormal corneal shape (to be newly named)
Brand Name	Suncon Kyoto-CS
Applicant	Sun Contact Lens Co., Ltd.
Date of Application	June 30, 2015
Proposed Intended Use	Correction of visual acuity in patients with an ocular sequela of Stevens Johnson syndrome or toxic epidermal necrolysis.

Items Warranting Special Mention Orphan medical device

II. Product Overview

Suncon Kyoto-CS is a limbal-supported, rigid contact lens indicated for patients with an ocular sequela of SJS or TEN, such as severe visual impairment and dry eye, resulting from severe scarring over the entire ocular surface and the rough and irregular corneal surface. The newly developed contact lens allows lacrimal fluid to enter between the lens and the cornea and smooth the irregular of the corneal surface to correct visual acuity. The product also suppress the evaporation of lacrimal fluid to alleviate symptoms of dry eye (Table 1).

Table 1. Image before and after wearing of Suncon Kyoto-CS

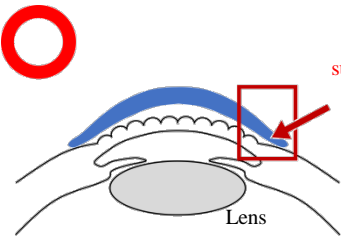
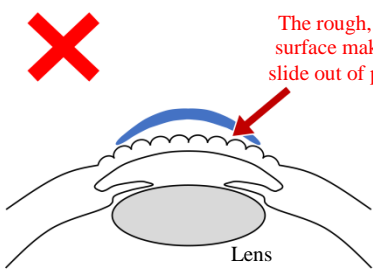
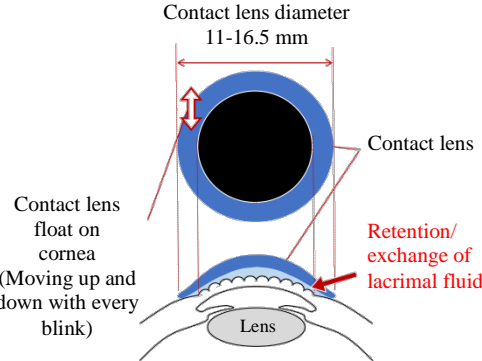
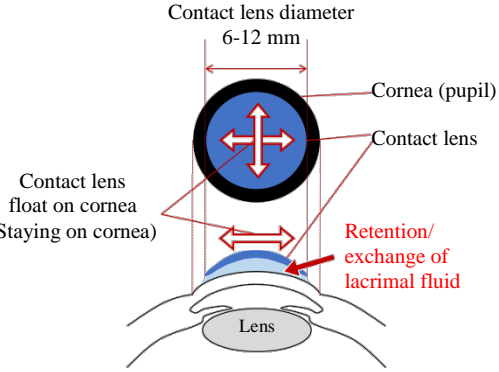
	Before wearing	After wearing
Mechanism of vision correction	 <p>Irregular astigmatism</p> <p>The rough, irregular corneal surface causes light scatter and reduced visual acuity.</p>	 <p>Retained lacrimal fluid</p> <p>Retained lacrimal fluid smooths the rough and irregular corneal surface and corrects visual acuity.</p>

Conventional rigid contact lenses (“corneal lenses”) are 6.0 to 12.0 mm in diameter, and are easy to slip out of the rough or dry ocular surface. Suncon Kyoto-CS, 11.0 to 16.5 mm in diameter, completely covers the cornea with its peripheral bevel designed to be placed on the limbal area to support the lens.

Suncon Kyoto-CS is characterized by its bevel gently curved in a multistage manner (Figure 1). The lens moves up and down at every blink while staying on the entire cornea, allowing lacrimal fluid to flow. The contact lens does not have to be removed before each instillation (Table 2).

The number of patients eligible for Suncon Kyoto-CS is estimated to be approximately 1000 to 1400 patients.^{1,2} In the current situation where there is no effective treatment that sufficiently alleviates the symptoms in patients with an ocular sequela of SJS or TEN, the device is expected to become an effective therapeutic option to improve the condition. Because of its particularly high demand in medical care and the possibility for its development, Suncon Kyoto-CS was designated as an orphan medical device on December 19, 2014.

Table 2. Comparison between Suncon Kyoto-CS and corneal lens

	Suncon Kyoto-CS	Corneal lens
Use in patients with an ocular sequela of SJS or TEN	 <p>The multi-stage-curved lens edge supports the lens at the limbal area.</p> <p>* The lens edge (the area in the red box in the illustration) is enlarged in Figure 1.</p>	 <p>The rough, dry ocular surface makes the lens slide out of place easily.</p>
Lens size and mechanism of retention and lacrimal fluid exchange achieved through lens movement	<p>Contact lens diameter 11-16.5 mm</p>  <p>Retention/exchange of lacrimal fluid</p> <p>Contact lens float on cornea (Moving up and down with every blink)</p> <p>Use in affected eye</p>	<p>Contact lens diameter 6-12 mm</p>  <p>Retention/exchange of lacrimal fluid</p> <p>Contact lens float on cornea (Staying on cornea)</p> <p>Use in healthy eye</p>

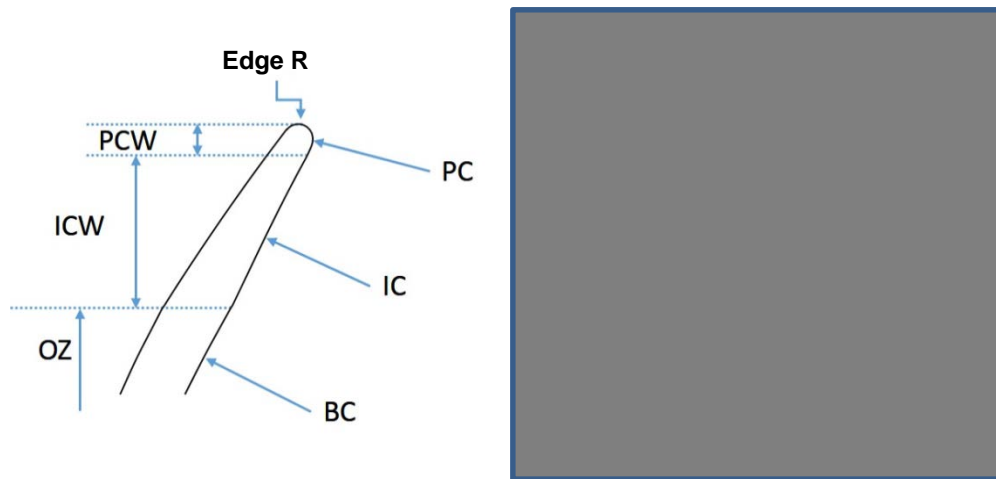


Figure 1. Bevel shape (left, corneal lens; right, Suncon Kyoto-CS)

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

The data submitted by the applicant with the application and the applicant’s responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors for the Expert Discussion on Suncon Kyoto-CS declared that it does not fall under Item 5 of the “Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 8/20 dated December 25, 2008).

1. History of development, use in foreign countries, and other information

1.(1) History of development

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

In patients with acute-phase SJS or TEN, extensive conjunctival or corneal epithelial defect causes corneal epithelial stem cell deficiency and makes epithelial repair difficult. Then, the conjunctival epithelium gradually covers the corneal surface, causing ocular sequelae including corneal opacity and irregular astigmatism and adhesion over the entire ocular surface. The ocular surface, including the cornea, becomes rough and irregular and causes light to scatter. This change causes decreased visual acuity, and insufficient lacrimal fluid makes the ocular surface dry all the time. An artificial lacrimal fluid or an ophthalmic solution such as hyaluronic acid can alleviate ocular pain or dry eye discomfort only transiently.³ It is thus extremely difficult to improve SJS- or TEN- associated visual acuity because of no established radical treatment. Full-thickness corneal transplant and lamellar keratoplasty often cause epithelial defects and therefore have limited therapeutic effects. Limbal transplant is effective but is known to have poor long-term prognosis causing uncontrollable inflammation several years later that may gradually aggravate. Transplant of cultivated oral mucosal epithelial sheets, which is still in a laboratory stage, is expected to improve visual acuity of <0.01 to 0.01 to 0.09 but not further than that even using a visual correction lens, and therefore patients still face difficulties in their daily lives.⁴ A newly invented method is a visual correction by covering the cornea with a contact lens. However, conventional soft contact lenses do not satisfactorily correct corneal irregular astigmatism. Because

common corneal lenses are too small to completely cover the irregular cornea, the lens stays on top of the cornea, which is too painful to keep. Outside Japan, a larger type of lens (hereinafter referred to as the “scleral lens”) is available for the correction of visual acuity in patients with a severely deformed cornea. Being larger than Suncon Kyoto-CS, the lenses can cover the conjunctiva on the sclera, but is not suitable for patients suffering severe adhesion between the back of the upper eyelid and the sclera.

To solve these problems, the applicant developed a rigid contact lens for patients with corneal epithelial stem cell deficiency, including ocular sequelae of SJS or TEN. The sizes and shape of the lens are tailored to this particular patient population so that it can be used even by those who suffer extensive and severe scarring over the entire ocular surface.

Corneal lenses are 6.0 to 12.0 mm in diameter and are put on the cornea. Because blinking causes vertical movement of the contact lens, the lens needs to be fitted so that the lens moves back to the cornea even from the conjunctiva. Optimal lens fitting allows for adequate movement, which provides sufficient lacrimal fluid exchange. Lacrimal fluid supplies oxygen and nutrients and eliminates waste products, etc. Suncon Kyoto-CS, on the other hand, is 11.0 to 16.5 mm in diameter, which completely covers the cornea and is supported by its bevel positioned to the limbal area. Its vertical movement at each blink promotes lacrimal fluid exchange. The contact lens covers the cornea all the time even during vertical movement. An artificial lacrimal fluid is instilled before wearing of Suncon Kyoto-CS, and it flows toward the cornea through lacrimal fluid exchange and is pooled on the cornea. This mechanism allows lacrimal fluid to stay on the cornea even in a severely dry eye such as with SJS, eases sensation of a foreign body and corrects vision acuity. The bevel of the corneal lens consists of an interim curve (IC) and a peripheral curve (PC), [REDACTED], is manufactured according to these specifications (Figure 1).

The scleral lenses are indicated for severe dry eye, ocular surface disease, etc. and are approved only overseas. The scleral lens of 15.0 to 23.0 mm in diameter, larger than Suncon Kyoto-CS, is supported at the sclera. The scleral lens is fitted to the cornea as if it is a mold and prevents smooth lacrimal fluid exchange. As a result, an ophthalmic solution dropped into the concave side of the contact lens before wearing remains pooled on the cornea. For these reasons, the scleral lens needs to be removed from the eye with a special device several times a day (Figure 2).⁴

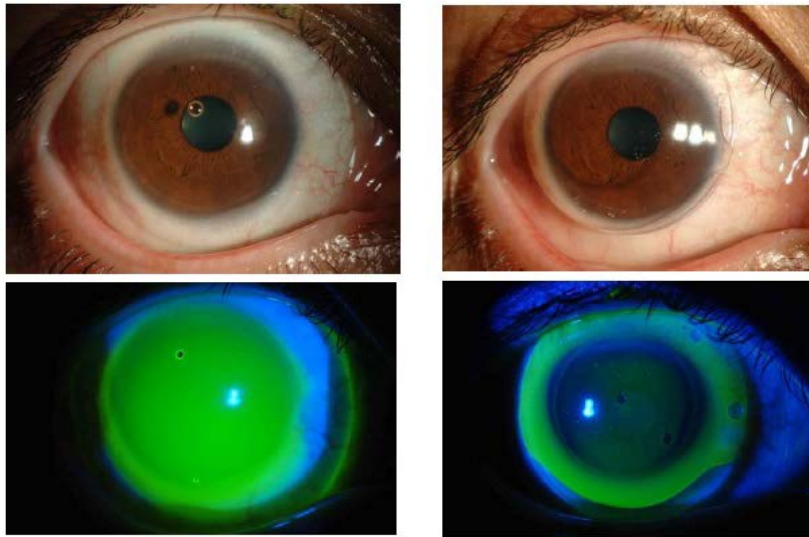


Figure 2. Contact lens in use (Left, scleral Lens; Right, Suncon Kyoto-CS)

Clinical research of Suncon Kyoto-CS was conducted at University Hospital, Kyoto Prefectural University of Medicine. The results demonstrated Suncon Kyoto-CS’s substantial effect to correct visual acuity by pooling lacrimal fluid between itself and the cornea that helps smooth the irregular corneal surface. The product also prevented evaporation of lacrimal fluid and reduced symptoms of dry eye. Of 65 eyes of 52 patients enrolled in the study research, 53 eyes of 42 patients had an ocular sequela of SJS. These patients achieved substantial improvement in visual acuity and QOL.⁴

Based on the results of the research, an investigator-initiated study was conducted at University Hospital, Kyoto Prefectural University of Medicine and Kyoto University Hospital. The results of this investigator-initiated study constitute the basis of the marketing application of the product.

1.(2) Use in foreign countries

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

Suncon Kyoto-CS is not approved or licensed in any foreign countries. Table 3 shows the shipping quantity of lens buttons, the raw material (“raw material buttons”) for scleral lenses used in patients with an ocular sequela of SJS or TEN reported for reference. As of April 2015, none of the malfunctions of scleral lenses on the market were attributable to raw material buttons.

Table 3. Shipping quantity of raw material buttons

Product name (Raw material name)	Boston XO (hexafocon A)	Boston XO2 (hexafocon B)	EqualensII (oprifocon A)
2012			
2013			
2014			

* Boston XO uses the same raw material as Suncon Kyoto-CS.

1.(3) Performance and safety specifications

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

The performance specifications of Suncon Kyoto-CS were defined based on Appendix 1 “Rigid Contact Lens Approval Standards” (“Rigid Contact Lens Approval Standards”) in the “Revision of the Contact Lens Approval Standards” (PFSB Notification No. 0428008 from the Pharmaceutical and Food Safety Bureau, MHLW dated April 28, 2009). The data submitted provide the justification of all these performance specifications of the product.

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

Unlike corneal lenses, Suncon Kyoto-CS is highly likely to be used with an artificial lacrimal fluid, antimicrobial agent, or steroid. PMDA asked the applicant to explain the necessity to investigate effects of these concomitant ophthalmic solutions on the product, in particular, deformity, deterioration, absorbed stains, testing on biological safety and strength using lens samples with their physicality substantially changed by eluted residual monomers, and ingredients of ophthalmic solutions attached onto their surfaces.

The applicant explained that the specifications were defined based on the compatibility test (deformity, deterioration, and stains) results of the ophthalmic solutions used in the clinical study.

PMDA has reviewed the additional specifications, including the performance specifications described in 2. “Data relating to design and development,” and concluded that there was no particular problem with the established specifications.

2. Data Relating to Design and Development

2.(1) Physicochemical properties

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

The submitted physicochemical data of Suncon Kyoto-CS were the results of the shape and appearance tests, allowance tests (diameter, thickness, base curve, vertex power, and prism error), and strength tests (compression-flexion test and impact strength test). All test results conformed to the defined specifications, assuring the physical properties of the product. The data relating to the luminous transmittance, refractive index, oxygen permeability, and chemical properties (residual monomers, coloring agents, the entire extractable substances, and eluates) are the properties of the raw material, and they were shown to be comparable with those of “Suncon Mild i (Approval number 22600BZX00040000),” which contains a larger amount of coloring agents than Suncon Kyoto-CS. Because of such equivalence, the data of “Suncon Mild i” were attached to the application for Suncon Kyoto-CS instead of conducting a new study on these properties with Suncon Kyoto-CS.

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

PMDA reviewed the physicochemical data and concluded that there was no particular problem with these properties.

2.(2) Electrical safety and electromagnetic compatibility

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

Since Suncon Kyoto-CS is not an electrical device, data relating to electrical safety and electromagnetic compatibility were not submitted.

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

PMDA concluded that there was no particular problem with not submitting data relating to electrical safety and electromagnetic compatibility.

2.(3) Biological safety

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

Suncon Kyoto-CS is used in patients with SJS or TEN. Presumably, patients in this population have different condition of the ocular surface from that of healthy adults. According to the “Basic concepts for evaluating biological safety of medical devices required for application of manufacturing/marketing approval” (PFSB/ELD/OMDE Notification No. 0301-20 of the Office of Medical Devices Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW dated March 1, 2012), biological safety studies require the evaluation of long-term contact of a surface contact device with a damaged surface. Because this requires the same evaluation as that for a long-term contact of a surface contact device with the mucosa, the applicant submitted the study data of “ [REDACTED] (Approval number [REDACTED])” manufactured by [REDACTED] using comparable raw materials and the same manufacturing process as Suncon Kyoto-CS, for extrapolation into the biological safety evaluation of Suncon Kyoto-CS. As part of risk analysis, data on the recent shipping quantity and malfunctions with the raw material button of the scleral lens, which is the same as that of Suncon Kyoto-CS, were reported. Approximately [REDACTED] raw material buttons are marketed per year for the production of the scleral lens, with no biological safety-related malfunctions attributable to the raw material.

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

The study results of “[REDACTED]” can be extrapolated to Suncon Kyoto-CS, because the biological safety of devices involving long-term contact with a normal mucosa and those involving long-term contact with a damaged surface are assessed by common criteria. No particular problem was identified in the study results of “[REDACTED]”. PMDA has concluded that there is no particular concern about the biological safety of Suncon Kyoto-CS.

2.(4) Stability and durability

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

Stability of Suncon Kyoto-CS was determined as >3 years based on that of “Suncon Mild i” because of their similarities in raw materials and production process. The stability data of Suncon Kyoto-CS were not submitted in light of the notification of “Dealing with stability studies for the application for marketing approval (certification) of medical devices in terms of expiry date setting” (PFSB/ELD/OMDE Notification No. 1227-5 of the Office of Medical Devices Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW dated December 27, 2012).

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

Because Suncon Kyoto-CS is produced with similar raw materials and by the same process as “Suncon Mild I,” PMDA agrees that Suncon Kyoto-CS has stability and durability in repeated use comparable to those of “Suncon Mild I,” which is a corneal lens available in market without any reported malfunctions associated with poor durability in repeated use. Since the clinical study showed no concern about durability and many patients used Suncon Kyoto-CS for ≥ 3 years in the preceding clinical research, PMDA concluded that Suncon Kyoto-CS is durable enough to raise no clinical concern.

2.(5) Performance

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

The submitted performance data were the results of compatibility with concomitant ophthalmic solutions. The compatibility of Suncon Kyoto-CS was tested with the following ophthalmic solutions: an agent for conjunctival or corneal epithelial damage, broad-spectrum antibacterial agent, anti-inflammatory steroid in aqueous suspension, dry eye agent, antibiotic preparation, agent for glaucoma/ocular hypertension, cephem antibiotic, and mucin secretagogue. Suncon Kyoto-CS was immersed in these solutions for a prespecified duration that provided a more extreme condition than when the product is usually used with each solution, and deformity, deterioration, and stains were investigated. The product was shown to conform to the determined specifications in the presence of any of these ophthalmic solutions.

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

The product’s compatibility was tested with ophthalmic solutions which are likely to be used with the product. The test method was designed with instillation frequency taken into consideration. Therefore, PMDA considers that the selection of ophthalmic solutions and test method were appropriate. On the other hand, deformity, deterioration, and stains were checked in terms of the base curve, vertex power, diameter, central thickness, and stain only. PMDA asked the applicant whether these test items suffice to detect deformity, deterioration, and stains.

The applicant’s explanation:

For the detection of deformity, deterioration, stains, etc., shape and appearance (for stains on the surface) was checked with a 10-fold magnifier according to the Rigid Contact Lens Approval Standards. The base curve, that is the curvature radius of posterior optical center of the lens, is distorted when its material deforms or deteriorates and becomes unmeasurable. However, the compatibility test results were all within the allowable range (± 0.05 mm) defined in the Rigid Contact Lens Approval Standards, showing that Suncon Kyoto-CS is free from deformity/deterioration (degeneration). Some lens samples were found to have minute stains on their surfaces at the end of the tests (Flumetholon Ophthalmic Suspension 0.1%, Diquas Ophthalmic Solution 3%, Ophthalon Ophthalmic Solution, and Mikelan LA Ophthalmic Solution 2%). However, they were free from deformity/deterioration (degeneration), indicating no reaction of the raw material polymer of the contact lens with any ingredient of the ophthalmic solutions. A total of 53 eyes of 42 patients had no problem attributable to these ophthalmic

solutions. Even stains temporarily remaining on lens surfaces can be removed using the care products for Suncon Kyoto-CS (scrubbing with enzyme-contained cleansing/preservative solution + soaking) unless the stains denature the lens. For these reasons, there is no problem about the combination use of the product with an ophthalmic solution.

PMDA asked the applicant to explain the risk for the adsorption of any ingredient of the ophthalmic solutions into the contact lens and the effects of such absorption, if any, on safety.

The applicant's explanation:

Hyalein Mini Ophthalmic Solution 0.3%, an ophthalmic solution for the treatment of conjunctival or corneal epithelial damage, is frequently used among patients suffering SJS. This preservative-free ophthalmic solution poses no risk for preservative ingredients to be absorbed. The main ingredient of this ophthalmic solution is sodium hyaluronate and is a water-soluble polymer with a mean molecular weight of 500,000 to 1,200,000. Because of these properties, this ingredient is unlikely to be adsorbed to the lens. The test revealed no change in lens surfaces, base curves, and in other specifications, indicating no absorption of any ingredient of the ophthalmic solutions to the lens surface. On the other hand, the following ophthalmic solutions other than that for conjunctival or corneal epithelial damage are used infrequently and in a short period: broad-spectrum antibacterial agent, anti-inflammatory steroid in aqueous suspension, agent for dry eye, antibiotic preparation, agent for glaucoma/ocular hypertension, cephem antibiotic, and mucin secretagogue. Usually, patients are instructed to instill an ophthalmic solution after they remove the contact lens, and then put the lens in the eye in 5 to 10 minutes after instillation. After instillation, 15% of the drug is cleared per minute. Since a ≥ 5 -minute interval is required between instillation and lens insertion, the contact lens will not be exposed directly to the ophthalmic solution for an extended period. The tests revealed no change on lens surfaces, base curve, and in other specifications after direct exposure to the ophthalmic solutions, indicating no absorption of any ingredients and hence no effects of absorption on safety. Suncon Kyoto-CS is a rigid contact lens and, unlike soft contact lenses, there is no possibility that the material of lens itself is not associated with absorption uptake. Time for direct exposure was longest with the ophthalmic solution for conjunctival or corneal epithelial damage. Except its main active ingredient of sodium hyaluronate, other ingredients are almost the same as those of physiological saline. No residual monomer was therefore detected in the extract in purified water in the test for chemical requirements, indicating no concern about the elution of residual monomers.

PMDA's view:

On the basis of the applicant's explanation, despite slight stains seen on the lens surface at the end of the tests, the raw material polymer of the contact lens is unlikely to react with any ingredients of the ophthalmic solutions tested because no deformity/deterioration (degeneration) was observed. The stains can only be explained by the adhesion of some ingredients of the ophthalmic solutions. In actual use, similar types of stains will be much less and, if any, can be removed by normal lens care because ophthalmic solutions other than that for conjunctival or corneal epithelial damage are used infrequently and usually patients are instructed to instill ophthalmic solutions after removing the contact lens and

then to insert the lens after a 5- to 10-minute interval. Even after Suncon Kyoto-CS was immersed in the ophthalmic solution for conjunctival or corneal epithelial damage, no residual monomer was detected in the extract in purified water. Because these findings indicate that the ophthalmic solutions will not deteriorate the contact lens, the use of the product with an ophthalmic solution will not pose particular problems.

2.(6) Directions for use

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

A usage verification study of Suncon Kyoto-CS was considered unnecessary. Data relating to the usage were not submitted.

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

Because Suncon Kyoto-CS is corneal ring-supported, removing the product from eye may not be as easy as with common corneal lenses. A plunger may be used as an aid in a similar way that is used to remove a standard corneal lens when it does not come out of eye easily. The use of a plunger for lens removal will be advised and the method of lens removal will be shown in the user's manual. The clinical research and study revealed no malfunctions of the product including damage upon insertion or removal. PMDA considered that a study to verify the usage of Suncon Kyoto-CS is unnecessary.

3. Conformity to the requirements specified in paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics

3.A Summary of the data submitted

A declaration of conformity declaring that the product 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 Pharmaceuticals, Medical devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics the Pharmaceutical Affairs Act (hereinafter referred to as "old Essential Principles"ⁱ) (MHLW Ministerial Announcement No. 122, 2005) was submitted.

3.B Outline of the review conducted by PMDA

The application for marketing approval of Suncon Kyoto-CS was submitted after the enforcement of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. That was however the interim measure period (until November 24, 2015) following the implementation of new Essential Principles for medical devices (November 25, 2014). According to the Notification No. 1105-5 of the Counselor of Minister's Secretariat, MHLW dated November 5, 2014, the old Essential Principles is applicable to products submitted during the interim measure period. Therefore, PMDA reviewed the submitted data for the conformity of Suncon Kyoto-CS to the old Essential Principles.

ⁱ Differences between the old and new Essential Principles: changes and additions were made regarding considerations for design and manufacture, considerations for use environment, considerations for medical devices using program, considerations for medical devices intended for use by lay persons, and information to be provided to users by labels or other materials.

Article 1 includes preconditions for designing medical devices (particularly, the requirements for users, such as expected level of technical knowledge and experience, and expected level of education and training to be provided to users). As explained in “6.B.4 Safety” and “6.B.5 Information provision regarding lens prescription” of “6.B Outline of the review conducted by PMDA,” fitting of the product at prescription is critical, and choice of a trial lens and fitting largely depend on knowledge and skills acquired by prescribing physicians. Concluding that the evaluation items initially determined by the applicant are not enough to demonstrate conformity to Article 1, PMDA instructed the applicant to take necessary measures and the applicant agreed.

Based on the above, PMDA has comprehensively reviewed the conformity of Suncon Kyoto-CS to the Essential Principles and concluded that there is no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management, the risk management system, and its implementation status in reference to ISO14971 “Medical devices - Application of risk management to medical devices.”

4.B Outline of the review conducted by PMDA

PMDA reviewed the document on risk management and concluded that there was no particular problem.

5. Manufacturing process

5.A Summary of the data submitted

The applicant submitted quality control data for the evaluation of manufacturing process of Suncon Kyoto-CS. Since the product is a non-sterile product, data on the sterilization method were omitted.

5.B Outline of the review conducted by PMDA

PMDA has reviewed the data on manufacturing process and concluded that there was no particular problem.

6. Clinical data or alternative data accepted by Minister of Health, Labour and Welfare

6.A Summary of the data submitted

The applicant submitted the results of an investigator-initiated clinical study in Japan, a prospective, multicenter, single-arm study to evaluate the efficacy and safety of Suncon Kyoto-CS in 10 eyes of patients with an ocular sequela of SJS or TEN in 2 centers. The study started on June 4, 2014 (the date of receiving the first subject consent) and ended on December 17, 2014 (the date of completing the last subject follow-up).

Table 4 shows the study population, and the primary inclusion and exclusion criteria.

Table 4. Study population and key inclusion and exclusion criteria

Study population	<p>Patients with an ocular sequela of SJS or TEN</p> <hr/> <p>Patients were eligible for the study if the diagnostic criteria for SJS or TEN and all of the following conditions of an ocular sequela were met:</p> <p>(1) Suffering SJS or TEN for ≥ 1 year with a persistent eye disorder showing no reversal to the condition before the onset of SJS or TEN</p> <p>(2) Suffering an eye disorder that is not attributable to other ophthalmic diseases</p> <p>(3) ≥ 3 of the following conditions identified by an ophthalmological examination: Conjunctival invasion, stem cell deficiency, keratinization, symblepharon, positional anomaly of mucocutaneous transition, Meibomian gland dysfunction, and lacrimal punctum closure</p>
Primary inclusion criteria	<p>(1) An ocular sequela of SJS or TEN</p> <p>(2) BCVA of ≥ 0.01 and < 0.7</p> <p>(3) A result of Schirmer's test (Method I) of ≤ 5 mm</p> <p>(4) Aged ≥ 20 and < 75 years at enrollment</p> <p>(5) Capability to visit the outpatient clinic</p>
Primary exclusion criteria	<p>(1) Any of the following complications:</p> <ul style="list-style-type: none"> • Acute or subacute inflammation in the anterior part of the eye • Eye infection • Uveitis <p>(2) Any allergic disease severe enough to affect the use of the contact lens</p> <p>(3) Easy exposure to dusts or chemicals in living environment.</p> <p>(4) Difficulty in manual tasks including contact lens insertion.</p> <p>(5) A history of ocular surgery (e.g., surgery for cataract, glaucoma, etc., and corneal transplant) within the last 3 months.</p> <p>(6) A history of participation in the clinical research of CS-100 for the affected eye.</p>

The clinical study was conducted according to a Research Program on Overcoming Intractable Diseases “Development of a New Medical Device for Severe Erythema Multiforme Exudativum” supported by MHLW. The primary endpoint was “improvement in BCVA with the investigational contact lens.” The “Improvement” was defined as a decrease of ≥ 0.2 logMAR*¹ from the BCVA before wearing the study device to the BCVA at Week 13. The efficacy of Suncon Kyoto-CS was considered demonstrated when the improvement rate was $\geq 50.0\%$ (i.e., the majority of subjects can achieve the improvement). Eight of 10 subjects achieved the improvement at the improvement rate of 80.0%. No subjects experienced aggravation (Table 5).

Table 5. Results of primary endpoint and uncorrected visual acuity

	Baseline			Week 13			
	BCVA		Naked eye	BCVA			Naked eye
	Decimal visual acuity	logMAR visual acuity (1)	Decimal visual acuity	Decimal visual acuity	logMAR visual acuity (2)	(2) - (1)	Decimal visual acuity
A01	0.01	2.00	0.01	0.01	2.00	Unchanged	0.01
A02	0.15	0.82	0.15	0.8	0.10	Improved	0.4
A03	0.3	0.52	0.1	0.8	0.10	Improved	0.4
A04	0.05	1.30	0.05	0.5	0.30	Improved	0.06
A05	0.4	0.40	0.1	0.7	0.15	Improved	0.15
A06	0.02	1.70	0.02	0.03	1.52	Unchanged	0.02
A07	0.4	0.40	0.4	0.9	0.05	Improved	0.3
A08	0.3	0.52	0.3	0.9	0.05	Improved	0.3
B01	0.2	0.70	0.1	0.7	0.15	Improved	0.3
B02	0.03	1.52	0.03	0.5	0.30	Improved	0.1

*¹ logMAR, the angle θ (Figure 3) between 2 points that can be barely discriminated from one another with an eye is called minimum visual angle (minute), whose reciprocal is decimal visual acuity. For example, a slit (1.5 mm) of the standard Landolt ring can be identified by patients with a visual acuity of 1.0 from a distance of 5 m. logMAR is the logarithm of the minimum visual angle and is used in statistical calculation of visual acuity.

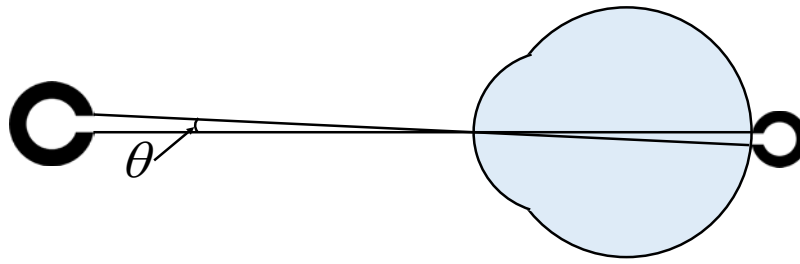


Figure 3. Visual angle and Landolt ring

Table 6. logMAR visual acuity

Decimal visual acuity	logMAR visual acuity	Decimal visual acuity	logMAR visual acuity	Decimal visual acuity	logMAR visual acuity
2.0	-0.30	0.5	0.30	0.06	1.22
1.5	-0.18	0.4	0.40	0.05	1.30
1.2	-0.08	0.3	0.52	0.04	1.40
1.0	0.00	0.2	0.70	0.03	1.52
0.9	0.05	0.1	1.00	0.02	1.70
0.8	0.10	0.09	1.05	0.01	2.00
0.7	0.15	0.08	1.10		
0.6	0.22	0.07	1.15		

Secondary endpoints were (a) a change in BCVA with the investigational contact lens, (b) a change in symptoms (NEI VFQ-25), and (c) a change in the severity of ocular pain and dryness (Verbal Rating Scale [VRS, a scale for medical interview] as modified Visual Analogue Scale).

- (a) The BCVA with the investigational contact lens improved at Week 13 with a change of 0.52 in the mean logMAR of all subjects. The improvement was significant ($P = 0.039$, Wilcoxon's signed rank test). The BCVA improved at each test point from Day 1 to Week 13.
- (b) The mean scores of all symptom subscales of NEI VFQ-25 at Week 13 were higher than those at baseline, showing improved QOL. Ocular pain and mental health due to the visual condition significantly improved ($P = 0.0078$ and 0.0039 , respectively, Wilcoxon's signed rank test).
- (c) The assessment using VRS are detailed in Table 7. "Improved" was defined as a ≥ 2 -level decrease in intensity after wearing the lens, "unchanged" as no change in score or a 1-level decrease in intensity, and "aggravated" as a ≥ 1 -level increase in intensity.

Table 7. Visual Rating Scale

Item	Criteria
Intensity of ocular pain	0: No pain 1: Some pain, ignorable 2: Some pain, occasionally annoying 3: Pain almost all the time, no difficulty in opening the eye 4: Severe pain, some difficulty in opening the eye 5: Severe pain, difficulty in opening the eye.
Intensity of ocular dryness	0: No dryness 1: Ignorable 2: Relieved with an artificial lacrimal fluid 3: Needs an artificial lacrimal fluid ≥ 6 times daily 4: Severe, needs an artificial lacrimal fluid at least once every hour. 5: Severe, causing difficulties in daily life even with the frequent use of an artificial lacrimal fluid

In the assessment using VRS, the intensity of ocular pain “improved” in 1 subject (10.0%), “unchanged” in 8 subjects (80.0%), and “aggravated” in 1 subject (10.0%). At baseline, ocular pain was rated as Intensity 1 (some pain, ignorable) in 7 subjects and as Intensity 0 (no pain) in 2 subjects. Of the 7 subjects had Intensity 1, 5 subjects achieved Intensity 0 (no pain) at Week 13, and 4 subjects had Intensity 0 even without the study device. The intensity of ocular dryness “improved” in 3 subjects (30.0%), “unchanged” in 3 subjects (30.0%), and “aggravated” in 4 subjects (40.0%). At baseline, ocular dryness was rated as Intensity 1 (ignorable) in 2 subjects and Intensity 2 (relieved with an artificial lacrimal fluid) in 3 subjects. Two subjects had a 1-level decrease in intensity from baseline during the use of the study device (Table 8).

Table 8. Intensity of ocular pain and dryness

	Improved (2-level decrease)	Unchanged	Aggravated
Intensity of ocular pain	1 (10.0%)	8 (80.0%) ^{*2}	1 (10.0%)
Intensity of ocular dryness	3 (30.0%)	3 (30.0%) ^{*3}	4 (40.0%) ^{*3}

^{*2} Because the baseline ocular pain was Intensity 1 (some pain, ignorable) in 7 subjects and Intensity 0 (no pain) in 1 subject, the achievement of “2-level decrease in intensity” was not possible for these subjects. Of the 7 subjects with Intensity 1, 5 subjects had Intensity 0 (no pain), including 4 subjects who had no pain even without the study device.

^{*3} Subjects were instructed to instill an artificial lacrimal fluid ≥ 6 times daily during the use of the study device. Consequently, these subjects were rated as Intensity 3 (needs an artificial lacrimal fluid ≥ 6 times daily.” Two of the 3 subjects had 1-level decrease in intensity.

The safety endpoints were adverse events, malfunctions, and others (effects of permitted concomitant drugs). Adverse events were reported by 5 subjects (6 cases); 3 cases of conjunctival erosion in 2 subjects (20.0%), 2 cases of eye discharge in 2 subjects, and 1 case of blepharitis in 1 subject. Adverse events with a suspected causal relationship to the study device included 3 cases of conjunctival erosion in 2 subjects, which were causally related to the study device, and 1 case of eye discharge in 1 subject, whose causality was unknown. No malfunctions occurred. Permitted concomitant drugs, including artificial lacrimal fluid, hyaluronic acid, antibacterials, and steroids, did not cause deformity or deterioration of the study lens, or adsorption of stains to the study lens.

6.B Outline of the review conducted by PMDA

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

- (1) Clinical positioning
- (2) Appropriateness of the clinical study design
 - 1) Rationale for endpoints
 - 2) Rationale for sample size

- 3) Use of a control group
- 4) Duration of evaluation
- (3) Efficacy
 - 1) Reason why 2 subjects failed to achieve improvement in BCVA in the clinical study
 - 2) Difference between NEI VFQ-25 and VRS results on ocular pain, a secondary efficacy endpoint
 - 3) “Severity of ocular dryness” in VRS, a secondary efficacy endpoint
- (4) Safety
- (5) Information provision regarding lens prescription

6.B.(1) Clinical positioning of Suncon Kyoto-CS

PMDA’s view on the clinical positioning of Suncon Kyoto-CS:

SJS or TEN does not always cause eye disorders. According to the additional research (2005 to 2007) and the follow-up research (2008 to 2010) focusing on ophthalmology in the Epidemiological Study by Severe Drug Eruption Research Group as part of Research Program on Intractable Diseases, 70% of patients experienced eye disorder in the acute stage of SJS or TEN. The additional research conducted by the above research group also revealed that the incidence of ocular sequelae in the chronic stage was approximately 15.6% of that in the acute stage in patients with BCVA of <0.9 and 2.2% in patients with BCVA of <0.1.¹

The major symptoms in patients with an ocular sequela of SJS or TEN are visual impairment, and dryness, pain, and discomfort in the eyes due to decreased lacrimal fluid. Dry eye-associated pain and discomfort are treated with an artificial lacrimal fluid or hyaluronic acid. However, it is difficult to resolve all these uncomfortable symptoms. For visual impairment, full-thickness corneal transplant, lamellar corneal transplant, limbal transplant, and cultivated oral mucosal epithelial sheet are prescribed, but patients receiving these treatments still have a poor long-term prognosis or fail to achieve sufficient visual acuity.⁴ Patients with an ocular sequela of SJS or TEN, for which Suncon Kyoto-CS is indicated, suffer corneal irregular astigmatism resulting from corneal shape anomaly. This type of irregular astigmatism cannot be corrected with a conventional soft contact lens and a contact lens easily comes off because of decreased lacrimal fluid. Corneal lenses are too small to completely cover the irregular cornea and thus inevitably placed on the cornea, which causes too much pain to wear it. In addition, the corneal lenses also easily come off because of decreased lacrimal fluid.

Suncon Kyoto-CS is indicated for patients who cannot achieve sufficient visual acuity with conventional eyeglasses, corneal lenses, or soft contact lenses because of an ocular sequela of SJS or TEN. PMDA has concluded that it is clinically significant to make Suncon Kyoto-CS available in clinical practice if it is shown to have a clinically acceptable efficacy and safety profiles.

6.B.(2) Appropriateness of the clinical study design

6.B.(2).1 Rationale for endpoints

The applicant’s explanation about the primary and secondary efficacy endpoints selected for the clinical study:

For patients with an ocular sequela of SJS or TEN, severe visual impairment is an obstacle to social rehabilitation. The clinical significance of Suncon Kyoto-CS can be evaluated based on improvement in

visual acuity with correction with the contact lens in patients with severe visual impairment. A 5-m eye chart is used to examine patients' far-point visual acuity, whose results are used for the evaluation of visual acuity. The examination is performed by an orthoptist according to the prespecified procedures so that errors and biases are minimized. In prescribing Suncon Kyoto-CS, the physician determines a lens design (e.g., diameter and base curve) by using a trial lens(s) and the degree of correction by performing visual acuity tests using trial eyeglasses. In general, improvement in visual acuity is assessed based on BCVA with consideration the characteristics of the subject.

There is no established consensus about to what degree of change in visual acuity should be regarded as "improvement" in the preceding research on serious anterior eye diseases such as SJS. The research in adults without eye disease or patients with eye disease revealed that a change of ≥ 0.2 logMAR is required to maintain good sensitivity and specificity and that even stable patients show a change of 0.16 logMAR. According to these findings, "improvement" was defined as a decrease of ≥ 0.2 logMAR. Because no other treatment is available for this disease, improvement achieved by $\geq 50\%$ of patients at Week 13 is of clinical significance.

Severe dry eye, an ocular sequela of SJS or TEN, causes persistent pain and other uncomfortable symptoms. To assess improvement in symptoms, NEI VFQ-25 was measured as a secondary endpoint before and after wearing the study device to confirm an increase in score. In addition, to assess alleviation of pain and dryness in the eyes, the results of subject's medical interview were evaluated using VRS, a modified VAS.

PMDA's view:

For statistical assessment, subjects with a baseline BCVA of ≥ 0.01 and < 0.7 were selected for this clinical study. After the market launch, Suncon Kyoto-CS may be used in patients with worse visual acuity. Many patients for whom this Suncon Kyoto-CS will be prescribed have corneal irregular astigmatism, which limits visual correction with eyeglasses. In addition, shape anomaly over the entire ocular surface makes the use of a corneal lens or soft contact lens difficult and prevents sufficient visual acuity correction. Since Suncon Kyoto-CS is used in patients who fail to achieve sufficient visual acuity correction by the conventional methods, the use of BCVA is appropriate to demonstrate the superiority of Suncon Kyoto-CS to the conventional methods in terms of visual acuity correction. It is also reasonable to define "improvement" as a decrease of ≥ 0.2 logMAR in comparison between before and after wearing the lens because a change of ≥ 0.2 logMAR is reportedly required to maintain good sensitivity and specificity although no consensus has been established as to what degree of change in visual acuity should be regarded as "improvement" in serious anterior eye diseases such as SJS, and taking account of the comments from the Expert Discussion.

On the basis of the above discussion, PMDA has concluded that it is appropriate to use BCVA to compare Suncon Kyoto-CS and the conventional methods in terms of visual acuity correction considering the patient's preference after wearing and agreed on the applicant's explanation. Because the preceding clinical research reported improved NEI VFQ-25 score and subjects' opinions indicating alleviated

ocular pain and dry eye sensation, PMDA has also concluded it is reasonable to add NEI VFQ-25 and VRS as secondary endpoints to assess the above parameters.

6.(B).(2).2) Rationale for sample size

The applicant's rationale for the sample size of 10 eyes:

According to Pharmaceuticals and Medical Devices Safety 84 patients (3.5%) had a sequela and of 1505 patients with a serious drug-induced skin disorder occurring from August 1, 2009 to January 31, 2012, 31 patients (2.1%) had a sequela. Although the percentage of visual impairment in all sequelae is unknown, several percent of patients are estimated to have visual impairment as a sequela, considering that outcome is unknown in $\geq 20\%$ of patients. For this reason, based on the number of evaluable patients in the clinical study, the sample size of 10 is considered reasonable for the conduct of study throughout the planned enrollment period. On the other hand, when the sample size is statistically calculated based on a change in BCVA with the investigational contact lens as a secondary endpoint, a change from the BCVA before wearing the lens to the BCVA at Week 13 needs to be evaluated. Based on a power of 80% and a significance level of 10%, the difference between before and after wearing the lens is analyzed by one-sided Wilcoxon's signed rank test. The necessary sample size was estimated to be 8 from the clinical research data. Taking into account of possible premature withdrawal, 10 patients would make the evaluation feasible.

PMDA's view:

As discussed in "6.B.(2).1) Rationale for endpoints," the primary endpoint was improvement in BCVA with the investigational contact lens, which is defined as a decrease of ≥ 0.2 logMAR. The efficacy of Suncon Kyoto-CS was to be demonstrated by an improvement rate of $\geq 50.0\%$ (i.e., improvement achieved by the majority of subjects). If the sample size were determined statistically based on the primary endpoint, it would go beyond a feasible sizes for this orphan medical device. Therefore, there would be no choice but to determine the sample size based on the feasibility of the study.

6.B.(2).3) Use of a control group

The applicant's rationale for comparing BCVA between before and after wearing Suncon Kyoto-CS without using a control group:

Suncon Kyoto-CS allows lacrimal fluid to enter between itself and the cornea to smooth the irregular corneal surface and correct visual acuity. Therefore, the efficacy of Suncon Kyoto-CS can be evaluated based on BCVA before and after wearing the product. A clinically relevant improvement rate was determined as a criterion for confirming the clinical significance of Suncon Kyoto-CS according to the comments from the medical device strategy consultation. The efficacy of Suncon Kyoto-CS can be confirmed with the improvement rate exceeding this threshold.

PMDA's view:

Suncon Kyoto-CS is indicated for patients in the chronic stage of SJS or TEN. Visual acuity of these patients is unlikely to improve spontaneously because of an ocular sequela. Neither the disease nor the ocular sequela is likely to be exacerbated acutely. Suncon Kyoto-CS is prescribed to patients who do

not benefit from the conventional treatments. Therefore, the efficacy and safety evaluation of Suncon Kyoto-CS is feasible by comparing the patient's condition between before and after wearing the lens, even without conducting a controlled study.

6.B.(2).4 Duration of evaluation

The applicant's rationale for the duration of evaluation in the clinical study:

The preceding clinical research demonstrated improved visual acuity immediately after the start of using the study device and no further change in the improvement rate at Week 13. During the mean duration of 2 years, Suncon Kyoto-CS was used in 53 eyes of 42 subjects, and the only adverse event reported was corneal erosion in 1 subject. This outcome indicates that 13 weeks are long enough to evaluate the efficacy and safety of Suncon Kyoto-CS. One subject who was prematurely discontinued from the preceding clinical research also experienced an adverse event of corneal erosion, which resolved.

PMDA's view:

Patients eligible for Suncon Kyoto-CS are those who are in the chronic stage of SJS or TEN having a certain level of corneal and conjunctival stability. Suncon Kyoto-CS, when it is appropriately fitted to individual patient's eye, can improve their visual acuity immediately after the use. The preceding clinical research demonstrated the stable visual acuity after wearing. For these reasons, the duration of evaluation was appropriate.

6.B.(3) Efficacy

6.B.(3).1 Reason why 2 subjects failed to achieve improvement in BCVA in the clinical study

PMDA asked the applicant to explain the reason that BCVA of 2 of 10 subjects did not improve in the clinical study.

The applicant's explanation:

Subject A01:

BCVA as decimal visual acuity was 0.01 both before and after wearing Suncon Kyoto-CS, showing no improvement. This can be explained by disuse esotropia attributable to SJS suffering for ≥ 25 years since childhood. Although improvement in BCVA was unpromising, the subject was enrolled in the study at their earnest request and conformity to the inclusion criteria. Despite no improvement in BCVA, the subject was profoundly satisfied with less eye fatigue while using the product.

Subject A06:

BCVA as decimal visual acuity was 0.02 and 0.03 before and after wearing Suncon Kyoto-CS, respectively, resulting in a decrease of 0.18 logMAR. The subject had corneal stromal opacity with a severe vascular invasion into the pupillary zone, which explains the minimal improvement in visual acuity. However, the subject noted subjective improvement in vision.

PMDA's view:

Suncon Kyoto-CS may not have sufficient effect to improve visual acuity of patients suffering an ocular sequela of SJS or TEN with disuse strabismus and corneal stromal opacity, and this should be highlighted in the package insert. Appropriately responding to the PMDA's advice, the applicant added a note to the effect to the package insert.

6.B.(3).2) Gap between NEI VFQ-25 and VRS results on ocular pain, a secondary efficacy endpoint

The applicant's explanation about the gap between the results of NEI VFQ-25 and VRS, a secondary efficacy endpoint in the clinical study:

The intensity of ocular pain (VRS) is assessed based on an interview on ocular pain and everyday sensation. The assessment criteria are presented in Table 7.

For a NEI VFQ-25 assessment, the Japanese version of NEI VFQ-25, v. 1.4 (for interview) was used. The ocular pain score is calculated from the scores of Questions 4 and 19. Question 4 asks about pain or discomfort of the eye and surrounding area, while Question 19 asks the degree of disadvantage of pain or discomfort of the eye and surrounding area in daily activities. The levels are translated to numerical scores ranging from 0 to 100. The mean value is regarded as the score of ocular pain.

Each degree category of Questions 4 and 19 and its corresponding score are presented below.

- Question 4 How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)?

Severity	Score
1: None	100
2: Mild	75
3: Moderate	50
4: Severe	25
5: Very severe	0

- Question 19 How much does your pain or discomfort in or around your eyes keep you from doing what you'd like to be doing?

Severity	Score
1: All of the time	0
2: Most of the time	25
3: Some of the time	50
4: A little of the time	75
5: None of the time	100

A possible cause of the gap between the results of 2 types of assessments is the difference between the nature of question asking the "degree of ocular pain" (VRS) and that asking about "ocular pain" (NEI VFQ-25).

Table 9 presents "intensity of ocular pain" (VRS) and "ocular pain" (NEI VFQ-25) at baseline and Week 13 of wearing the study device of each subject. The following paragraphs explain a gap between the 2 types of assessments revealed in 4 subjects (A02, A04, A05, and B01).

Subject A02:

The subject had no pain before and after wearing Suncon Kyoto-CS, thus the intensity of ocular pain (VRS) remain as 0 (no pain). On the other hand, NEI VFQ-25 showed the score for pain or discomfort improved from 25 to 50 and the score for difficulty in doing everyday tasks because of pain or discomfort from 0 to 50, resulting in improvement in the average score from 12.5 to 50.0.

Subject A04

The intensity of ocular pain (VRS) decreased from 1 (some pain, ignorable) to 0 (no pain). On the other hand, the scores remain unchanged for pain or discomfort measured by NEI VFQ-25 at 75 and for difficulty in doing everyday tasks at 50. As a result, the mean score remain unchanged at 62.5, showing no improvement.

Subject A05:

The intensity of ocular pain (VRS) increased from 1 (some pain, ignorable) to 2 (some pain, occasionally annoying). NEI VFQ-25 revealed worsened score for pain or discomfort from 25 to 0 and improved score for difficulty in doing everyday tasks from 50 to 100. The mean score improved from 37.5 to 50.0.

Subject B01:

The intensity of ocular pain (VRS) remain unchanged from 1 (some pain, ignorable). On the other hand, NEI VFQ-25 showed improved scores for pain or discomfort from 50 to 75 and difficulty in doing everyday tasks from 75 to 100. The mean score improved from 62.5 to 87.5.

Table 9. Severity of ocular pain (VRS) and ocular pain (NEI VFQ-25) at baseline and Week 13 of wearing the study device by subject

Subject No.	Degree of ocular pain (VRS) Degree		Ocular pain NEI VFQ-25 score ([r Question 4 + Question 19]/2)			(NEI VFQ-25) Question 4 Pain or discomfort in and around the eyes				(NEI VFQ-25) Question 19 Difficulty in doing things as desired due to pain or discomfort in or around the eyes			
	Baseline	Week 13	Baseline	Week 13	Baseline		Week 13		Baseline		Week 13		
					Degree	Score	Degree	Score	Degree	Score	Degree	Score	
A01	1	0 Improved	50.0	62.5	Improved	3	50	2	75	3	50	3	50
A02	0	0 Unchanged	12.5	50.0	Improved	4	25	3	50	1	0	3	50
A03	1	0 Improved	50.0	75.0	Improved	3	50	2	75	3	50	4	75
A04	1	0 Improved	62.5	62.5	Unchanged	2	75	2	75	3	50	3	50
A05	1	2 Worsened	37.5	50.0	Improved	4	25	5	0	3	50	5	100
A06	1	0 Improved	50.0	62.5	Improved	4	25	2	75	4	75	3	50
A07	0	0 Unchanged	100.0	100.0	Unchanged	1	100	1	100	5	100	5	100
A08	1	0 Improved	50.0	75.0	Improved	3	50	2	75	3	50	4	75
B01	1	1 Unchanged	62.5	87.5	Improved	3	50	2	75	4	75	5	100
B02	3	0 Improved	50.0	100.0	Improved	3	50	1	100	3	50	5	100

PMDA's view:

The focus of VRS is ocular pain. NEI VFQ-25, on the other hand, is an international rating scale to assess the effects of visual impairment on normal daily activities. Question 4 of NEI-VFQ-25 asks about

pain and discomfort in and around the eyes in general, including painless conditions, while Question 19 asks how much the pain or discomfort in and around the patient's eyes affects their daily activities. In other words, NEI VFQ-25 is intended to assess patients' lives in general, not limiting its focus to pain, and is different from VRS that focuses on ocular pain only.

VRS strictly defines "improvement" as a ≥ 2 -level decrease in intensity. Many subjects enrolled in the clinical study had only slight pain at baseline, including those who could not achieve a 2-level decrease in intensity. Even a 1-level improvement was achieved by 6 of 10 subjects, and 3 subjects had no change. The inconsistency between the results of the 2 kinds of assessments may be attributable to the stringent definition of improvement in VRS that is limited to ≥ 2 -level decrease in intensity. Therefore, the use of Suncon Kyoto-CS is expected to reduce pain and improve patients' lives. However, the clinical study failed to demonstrate pain reduction clearly. PMDA concluded that pain should be further investigated in a use-results survey as explained below and instructed the applicant accordingly.

6.B.(3).3) Severity of ocular dryness in VRS, a secondary efficacy endpoint

The applicant's explanation about the worsening of ocular dryness in 4 subjects (40%) after wearing Suncon Kyoto-CS:

Levels of ocular dryness were assessed using VRS based on the frequency of instillation (Table 7). In the assessment, what was unexpected was difficulty in answering the questions for subjects when their situations with "dry eye sensation" and "frequency of instillation," were contradictory. All 10 eligible subjects had severe dry eye, but some of them had few symptoms and rarely used an ophthalmic solution. Those with infrequent instillation were instructed to instill an ophthalmic solution ≥ 6 times a day during the use of Suncon Kyoto-CS. Following the instruction, these subjects used an ophthalmic solution ≥ 6 times a day during the study, and consequently come to downgrade their rating of "ocular dryness" in VRS. While no subject had a negative results of NEI VFQ-25, VRS failed to yield results that reflect the true efficacy of Suncon Kyoto-CS, because of its scale setting that did not fit with subjects' clinical situations.

PMDA's view:

The clinical research was conducted without using VRS. Patients who had used Suncon Kyoto-CS reported reduced dryness, VRS was then introduced in the clinical study in an exploratory manner. Given the situation where there was no established rating method for dryness, lack of careful consideration cannot be denied. Six subjects (60%) had improved uncorrected visual acuity after wearing Suncon Kyoto-CS (Table 5). Probably, this is because lacrimal fluid was retained between the lens and the cornea to help smooth the fine irregular ocular surface epithelium. In addition, the results of fluorescein staining in the clinical research showed clearly that the specially designed lens margin promotes lacrimal fluid exchange. The results in theory support the assumption that Suncon Kyoto-CS reduces dryness, but it has not been clearly demonstrated. Therefore, dryness should also be investigated in the use-results survey as explained in a later section. PMDA instructed the applicant accordingly.

The above discussions support clear efficacy of Suncon Kyoto-CS in visual acuity correction. While the efficacy of the product on ocular dryness and pain remains unclear according to the VRS assessment,

NEI VFQ-25 showed improvement in these symptoms. Suncon Kyoto-CS is designed to promote lacrimal fluid exchange and it was demonstrated. In some subjects, their uncorrected visual acuity improved transiently, suggesting the possible improved dryness. Accordingly, Suncon Kyoto-CS may be intended not only for visual acuity correction but also for the alleviation of ocular symptoms.

6.B.(4) Safety

In the clinical study, the following adverse events occurred with a suspected causal relationship to Suncon Kyoto-CS: 3 cases of conjunctival erosion in 2 subjects and 1 case of eye discharge in 1 subject (Table 10). Because conjunctival erosion might have been attributable to non-optimal fitting of Suncon Kyoto-CS, PMDA asked the applicant to explain whether the lens was exchanged after the occurrence of conjunctival erosion and whether the event resolved. PMDA also asked the applicant to explain the necessity of taking some measure to treat eye discharge.

Table 10. Adverse events

Subject No. Affected eye	Adverse event Verbatim term in the case report (Preferred Term, MedDRA/J)	Onset date (time to onset) Outcome date (duration)	Severity Causality	Intervention
A06 Left eye	Epithelial defect at the use of the study device (Conjunctival erosion)	September 3, 2014 (15 days) September 24, 2014 (22 days)	Mild Related	Temporal discontinuation of the study device; Gatiflo Ophthalmic Solution, left eye, 4 times; Tarivid Ophthalmic Ointment, left eye, twice
	Epithelial defect during the use of the study device (left) (Conjunctival erosion)	November 17, 2014 (90 days) November 28, 2014 (12 days)	Mild Related	
A07 Right eye	Conjunctival epithelial defect at the use of the study device (Conjunctival erosion)	October 15, 2014 (57 days) October 22, 2014 (8 days)	Mild Related	Temporal discontinuation of the study device; Tarivid Ophthalmic Ointment, right eye, twice
A08 Left eye	Increased eye discharge at the use of the study device (Eye discharge)	October 22, 2014 (36 days) October 29, 2014 (8 days)	Mild	Bestron for Ophthalmic and Gatiflo Ophthalmic Solution, 5 times per day
			Unknown	

The applicant's explanation about the adverse events in the clinical study:

Conjunctival erosion

The 2 subjects experiencing conjunctival erosion (A06 and A07) presented with adhesions in the upper and lower conjunctival sacs, which were asymmetrical to each other. The adhesion was more severe in the upper conjunctival sac than in the lower conjunctival sac. The upper part of the eyeball was eroded. The erosion was probably caused by the pressure of the contact lens on the adhesion in the upper conjunctival sac when the eyeball moved upward at each blink (Bell's phenomenon). In other subjects, the severity of adhesions was similar between the upper and lower conjunctival sacs. The conjunctival erosion observed was therefore considered attributable to the severity of adhesion in the subjects suffered. Accordingly, the package insert should provide precautionary advice for the prescription of a lens to the effect that "careful attention is required to possible conjunctival erosion when the adhesions of the upper and lower conjunctival sacs are asymmetric and the conditions is more severe in the upper conjunctival sac than in the lower one." Conjunctival erosion should also be monitored through post-marketing surveillance.

Clinical course and interventions

Subject A06 (a) The event occurred on Day 15 (September 03, 2014) and resolved 22 days later (September 24, 2014).

The use of study device was temporarily discontinued. The subject was treated with Gatiflo Ophthalmic Solution 4 times and Tarivid Ophthalmic Ointment twice.

The size of the contact lens was changed after discontinuation. The use of the study device resumed with a lens of new size on September 24, 2014.

(b) The event occurred on Day 90 (November 17, 2014) and resolved 12 days later (November 28, 2014).

The subject was followed up without changing the size of the contact lens.

Table 11. Specifications of the contract lens used by Subject A06

	Base curve (mm)	Vertex power (D)	Diameter (mm)	Diameter of optical part (mm)	Bevel type
Before change	7.9	0.0	13.0	8.5	Normal
After change	7.8	-1.5	13.0	8.5	Normal

Subject A07 The event occurred on Day 57 (October 15, 2014) and resolved 8 days later (October 22, 2014).

The use of study device was temporarily discontinued. The subjects was treated with Tarivid Ophthalmic Ointment twice.

The size of the contact lens was not changed after removal. The use of the study device resumed on October 21, 2014.

Table 12. Specifications of the contract lens used by A07

Base curve (mm)	Vertex power (D)	Diameter (mm)	Diameter of optical part (mm)	Bevel type
8.2	0.0	13.0	8.5	Normal

Eye discharge

A08 frequently experienced increased eye discharge even before the use of the study device. The causality of the event was assessed as “unknown” because a causal relationship to the study device could not be ruled out. However, the event was probably attributable to their underlying disease. Increased eye discharge is a common symptom accompanying the underlying disease. Nevertheless, patients should be advised to consult their ophthalmologist for possible concomitant bacterial conjunctivitis when eye discharge increases with the use of the study device.

PMDA’s view:

The subjects who experienced conjunctival erosion in the clinical study had more severe adhesion in the upper conjunctival sac than that in the lower one, with more severe adhesion than other subjects. Therefore, the applicant’s observation that the contact lens probably pressed the upper part of the eyeball at each blink is appropriate.

Conjunctival erosion is commonly seen in patients with the target disease because of its characteristics. Conjunctival erosion develops depending on the condition of conjunctival adhesion and contact lens fitting. The applicant therefore included relevant precautions in the package insert. The applicant added conjunctival erosion and the change of lens size after onset of conjunctival erosion in a use-results survey as survey items. Furthermore, the package insert was modified with precautionary advice to prescribing physicians that patients should be instructed to consult their physicians for increased eye discharge. All these decisions and actions of the applicant are appropriate.

6.B.(5) Information provision regarding lens prescription

Appropriate lacrimal fluid exchange is achieved only with optimal fitting of the contact lens. Having said that, because of the abnormality in the cornea or conjunctiva due to SJS or TEN, proper fitting is more difficult with Suncon Kyoto-CS than with corneal lenses. PMDA asked the applicant to explain the frequency of trial lens replacement in the clinical study and the necessity of information provision based on the results of the clinical study and research.

The applicant's explanation about the frequency of trial lens replacement in the clinical study and information provision in prescribing the lens after the market launch:

Table 13 presents the details of trial lenses used on 8 eyes after the first prescription at University Hospital, Kyoto Prefectural University of Medicine. Because the recording of relevant data was not mentioned in the written instructions, 2 subjects (B01 and B02) enrolled in the study at the Ophthalmology Department of Kyoto University Hospital had no record on the use of trial lenses. Both subjects changed trial lenses 3 times. After the first prescription, the frequency of change of trial lenses for each of 8 eyes ranged from 1 to 6 times with the mean of 3.3 times.

Table 13. Trail lenses

Subject No.	Trail lens data						Prescription data					Frequency of insertion
	Trial No.	Base curve (mm)	Vertex power (D)	Diameter (mm)	Diameter of optical part (mm)	Bevel type	Base curve (mm)	Vertex power (D)	Diameter (mm)	Diameter of optical part (mm)	Bevel type	
A01	(1)	7.7	0.0	14.0	9.0	N	7.8	0.0	13.0	8.5	N*	3
	(2)	7.8	0.0	14.0	9.0	N						
	(3)	7.8	0.0	13.0	8.5	N						
A02	(1)	7.9	0.0	14.0	8.5	N	7.8	+2.0	14.0	9.0	N*	4
	(2)	7.9	0.0	14.0	9.0	N						
	(3)	7.8	0.0	14.0	9.0	N						
	(4)	7.7	0.0	14.0	9.0	N						
A03	(1)	7.9	0.0	14.0	8.5	N	7.9	0.0	14.0	8.5	N*	4
	(2)	7.8	0.0	14.0	8.5	N						
	(3)	8.0	0.0	14.0	8.5	N						
	(4)	8.0	0.0	14.0	9.0	N						
A04	(1)	7.9	0.0	14.0	8.5	N	7.8	-3.0	14.0	8.5	N*	1
A05	(1)	7.9	0.0	14.0	8.5	N	8.2	0.0	13.0	8.5	N*	3
	(2)	8.1	0.0	14.0	8.5	N						
	(3)	8.1	0.0	14.0	9.0	N						
A06	(1)	7.9	0.0	13.0	8.5	N	7.9	0.0	13.0	8.5	N*	1
A07	(1)	7.9	0.0	14.0	8.5	N	8.2	0.0	13.0	8.5	N*	6
	(2)	8.0	0.0	13.0	8.5	N						
	(3)	8.1	0.0	13.0	8.5	N						
	(4)	8.0	0.0	14.0	9.0	N						
	(5)	8.0	0.0	14.0	8.5	N						
	(6)	8.1	0.0	13.0	8.5	N						
A08	(1)	7.9	0.0	14.0	8.5	N	8.1	0.0	13.0	8.5	N*	4
	(2)	7.9	0.0	13.0	8.5	N						
	(3)	8.1	0.0	13.0	8.5	N						
	(4)	8.1	0.0	14.0	8.5	N						

*Bevel type, 2 types of bevel, Normal (N) and Tight (T), are available,

Corneal curvature values are hardly obtained from most patients eligible for Suncon Kyoto-CS. Even using a corneal topography, the selection of a trial lens is difficult. The prescription of the product is according to the corneal curvature if available. Otherwise the most common lens (with base curve of 780 or 790) is tried. Based on its fitting pattern, the second trial lens is selected. This process (selecting the next lens based on the current fitting pattern) is repeated until the prescription lens is finalized.

Lens fitting at prescription are to be detailed in the package insert. Organizing a post-marketing workshop is being planned for provision of further details.

Physicians should be well aware of the following for selecting a trial lens:

- (a) The corneal curvature can hardly be measured in most patients.
- (b) The amount of lacrimal fluid makes lens fitting look different.
- (c) When a contact lens is inserted, physiological saline, etc. should be instilled to check lens fitting.
- (d) Once the prescription lens is selected based on a trial lens(es), the patient should undergo a visual acuity examination, followed by another fitting check.

The applicant is planning to detail the methods of trial lens selection, one using the corneal curvature measured and another without the measurement.

PMDA's view:

Suncon Kyoto-CS is indicated for patients with an ocular sequela of SJS or TEN who can use neither soft nor rigid contact lens. Because of the characteristics of ocular sequelae of SJS or TEN, assessment of lens fitting quality is difficult at the time of prescription. Because poorly fitted trial lenses do not promote lacrimal fluid exchange, the use of such products leads to no improvement in visual acuity, causing conjunctival erosion or other adverse events in some cases. In the clinical study, 3 subjects underwent changes of the prescription lens 3 times due to poor fitting, and 1 subject experienced size change once due to conjunctival erosion. Suncon Kyoto-CS should be therefore appropriately prescribed by physicians who have knowledge on ocular sequelae of SJS or TEN and experience in prescribing of rigid contact lenses to patients suffering corneal shape anomaly. The product, therefore, should be approved on the condition mentioned later.

7. Plan for post-marketing surveillance etc. stipulated by Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the data submitted

The clinical study clearly demonstrated the primary endpoint of "improvement in BCVA with the investigational contact lens." Nevertheless, data collection will be continued through the use-results survey to elucidate the efficacy of the product with a certain degree of accuracy. To achieve an estimation with an accuracy of $\pm 10\%$, the target sample size was determined to be 70 eyes.

The secondary endpoints of changes in symptoms, the severity of ocular pain, and the severity of ocular dryness also improved. However, the available data were of only 10 subjects and were based on the criteria which may have been inadequate. The secondary endpoints will be investigated in the post-marketing use-results survey with modified criteria. To evaluate the product's safety at the same time, objective signs (conjunctival hyperaemia, corneal opacity, and intracorneal vascular invasion) will also be investigated in the survey.

The preceding 3-year clinical research targeted 53 eyes of 42 subjects. Accordingly, approximately 14 patients will be enrolled to investigate 18 eyes annually in the survey at University Hospital, Kyoto Prefectural University of Medicine. In the post-marketing phase, many other medical centers will participate in the survey. However, assuming that each center will be able to accept fewer number of patients than at University Hospital, Kyoto Prefectural University of Medicine, the reasonable sample size per year will be approximately 30 eyes. If the planned sample size is 70 eyes, data collection will take 2 years and 6 months. In terms of the reproducibility of the results of this clinical study, the appropriate observation period is 13 weeks.

7.B Outline of the review conducted by PMDA

Suncon Kyoto-CS is indicated for rare diseases. The product has rarely been used in and outside Japan, and only 10 patients were enrolled in the clinical study. Because the efficacy and safety of the product need to be further investigated, a use-results survey should be conducted in the sample size proposed by the applicant.

This clinical study did not elucidate the product's effect on the alleviation of dryness and accompanying pain. Because the symptoms of the disease have kept patients from wearing contact lenses, they are not get used to even the use of standard corneal lenses. Reduction in subjective dryness and pain and retention of corrected visual acuity should be assessed when the patient is get accustomed to wearing the product. The reasonable observation period of the use-results survey is 6 months, including time for the verification of the efficacy profile seen during the 13-week follow-up period of the clinical study and the safety profile that revealed the onset of an adverse event of conjunctival erosion on approximately Day 90 (Table 14).

Table 14. Outline of the modified use-results survey plan

Objectives	To verify the efficacy and safety of Suncon Kyoto-CS in patients with an ocular sequela of SJS or TEN
Planned sample size	70 eyes
Survey period	4 years Preparation for marketing, 6 months; patient enrollment, 2 years and 6 months; follow-up, 6 months; analysis, 6 months
Survey items	<ul style="list-style-type: none">• Visual acuity (uncorrected, corrected)• Objective signs (conjunctival hyperaemia, corneal opacity, and intracorneal vascular invasion)• Symptoms (dryness and pain in the eye)

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

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 Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. 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.

V. Overall Evaluation

Suncon Kyoto-CS is a limbal-supported, rigid contact lens indicated for patients with an ocular sequela, such as severe visual impairment and dry eye, resulting from severe scarring over the entire ocular surface and the rough and irregular corneal surface due to SJS or TEN. The regulatory reviews of the product were focused on (1) the descriptions of efficacy and intended use, (2) safety, (3) information provision on lens prescription, and (4) use results evaluation. Based on comments from the Expert Discussion, PMDA reached the following conclusions:

(1) Descriptions of efficacy and intended use

The assessment of the primary efficacy endpoint of the clinical study revealed that a decrease of ≥ 0.2 logMAR was achieved in 8 of 10 subjects with the improvement rate of 80.0%. The remaining 2 subjects who failed to achieve a decrease of ≥ 0.2 logMAR showed no aggravation. The mean decrease in logMAR in 10 subjects was 0.52, which was significant ($P = 0.039$, signed rank test). The result sufficiently demonstrated the efficacy of Suncon Kyoto-CS in visual acuity correction. Secondary efficacy endpoints, ocular pain and dryness assessed using VRS did not show the effects clearly. The study enrolled patients without baseline severe ocular pain, and “Improvement” was defined as a ≥ 2 -level decrease in intensity. For these reasons, the study failed to show a clear effect of the product on improvement in ocular pain. However, 6 subjects (60.0%) achieved a 1-level improvement and NEI VFQ-25 assessing the effect of visual impairment on normal daily activities indicated a significant improvement in the severity of ocular pain. Suncon Kyoto-CS allows lacrimal fluid to stay between itself and the corneal and promotes lacrimal fluid exchange at each blink. Fluorescein staining clearly demonstrated lacrimal fluid exchange with every blink, and temporal improvement in uncorrected visual acuity was observed in some subjects. The product thus has a possibility to alleviate dryness in theory. Because the design of Suncon Kyoto-CS is intended to alleviate symptoms including ocular pain, PMDA has concluded that “alleviation of symptoms” can be written as an additional intended use besides visual acuity correction.

(2) Safety

Adverse events with a suspected causal relationship to Suncon Kyoto-CS were 3 cases of conjunctival erosion in 2 subjects (20.0%) and 1 case of eye discharge in 1 subject (10.0%). One of the 3 cases of conjunctival erosion involved a change of the lens specifications. These 2 subjects had asymmetric adhesion of the upper and lower conjunctival sacs. These cases were appropriately communicated, and the occurrence of conjunctival erosion and change in the lens size after the event were added in the use-results survey as survey items. The duration of follow-up was extended to 6 months to assess these additional survey items. Further, additional guidance was given to physicians in the package insert to the effect that patients should be instructed to consult their physician if eye discharge increases. PMDA concluded that these applicant’s actions are appropriate.

(3) Information provision regarding lens prescription

The trial lenses were worn on 8 eyes during the first prescription 1 to 6 times (mean, 3.3 times). After prescription, the trial lenses for 3 eyes underwent specification changes for 3 times. One of these cases was due to conjunctival erosion, and the remaining 2 cases were due to poor fitting or discomfort during the use of the lens. Because of the morphological characteristics of the anterior part of an eye with ocular sequelae of SJS or TEN, lenses can hardly fitted during prescription. A poorly fitted lens is an obstacle to lacrimal fluid exchange, failing to increase visual acuity or causing discomfort and adverse events such as conjunctival erosion. PMDA therefore concluded that Suncon Kyoto-CS should be appropriately prescribed by physicians who have knowledge on ocular sequelae of SJS or TEN and experience of prescribing rigid contact lens to patients with corneal shape anomaly.

(4) Evaluation of use results

Suncon Kyoto-CS is indicated for rare diseases. There is only limited experience in its use in Japan and overseas. The efficacy and safety of Suncon Kyoto-CS must be further investigated through a use-results survey.

The effects of the product to reduce dryness and accompanying pain were not clearly proven in the clinical study. These changes must be assessed based on symptoms and corrected visual acuity retained when the patient get accustomed to wearing the lens. The monitoring for conjunctival erosion requires on approximately Day 90 to verify the safety profile of the product. Thus, follow-up of each patient should be continued for 6 month. The duration of the use-results survey should be 4 years, which include 6 months to prepare for the launch, 2 years and 6 months to enroll patients, 6 months to follow the last patient, and another 6 months to collect survey forms for analyses.

Based on the above discussions, PMDA concludes that the product may be approved for the intended use modified as below and with the following condition of approval.

Intended Use

Correction of visual acuity and alleviation of symptoms in patients with an ocular sequela of Stevens Johnson syndrome or toxic epidermal necrolysis who do not achieve satisfactory visual acuity using conventional eye glasses or contact lenses.

Condition of Approval

The applicant is required to cooperate with related academic societies and take necessary actions to ensure the proper use of the product. For instance, knowledge and skills training may be provided to prescribing physicians, who must have established knowledge and experience in treating conditions relevant to the indication for the product, so as to enhance their prescription skills.

The product is not classified as a biological product or a specified biological product. The product should be designated as a medical device subject to the use-results survey. The duration of the use-results survey should be 4 years.

PMDA concludes that this application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

References

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