or at a different medical facility. Corneal reconstruction was performed in 21 eyes: COMET in 9 eyes, cultivated limbal epithelial transplantation in 5 eyes, limbal transplantation or keratoepithelioplasty in 5 eyes, and penetrating keratoplasty or lamellar keratoplasty in 6 eyes. Conjunctival reconstruction was performed in 17 eyes: amniotic membrane transplantation in 11 eyes, COMET in 2 eyes, oral mucosal transplantation in 2 eyes, and other surgeries in 2 eyes. Cataract surgery was performed in 13 eyes. Entropion surgeries were performed in 12 eyes, and ptosis surgeries were performed in 4 eyes. Fitting and use of the limbal CL was initiated only when the ocular surface had been stable for at least 1 month after cataract or eyelid surgery and for at least 3 months after ocular surface reconstruction or keratoplasty.

• OCULAR SURFACE GRADING SCORE: As reported previously, the ocular surface grading score reflects the severity of sequelae caused by SJS or TEN.[36] The loss of the palisades of Vogt and meibomian gland involvement were grade 3 in 50 eyes (94.3%) and 51 eyes (96.2%), respectively. That is, more than 95% of eyes were limbal stem cell deficient and also had severe meibomian gland dysfunction. Mild to moderate neovascularization and opacification of the cornea existed (Supplemental Table, available at AJO.com).

There were 11 eyes in group 1, 31 eyes in group 2, and 11 eyes in group 3. All ocular surface grading scores (except those for hyperemia and punctal damage), as well as the total score, were highest in group 1 and lowest in group 3 (Table 1).

• TEAR EXCHANGE UNDER THE CONTACT LENS: The results of the tear-exchange experiment revealed substantial differences in fluorescein staining patterns and concentrations between the scleral CL and the limbal CL. Fluorescein patterns showed no change of fluorescein concentration over a 10-minute period in the eyes with the scleral CL, but did reveal a gradual decrease of fluorescein concentration in the eyes with the limbal CL (Figure 3).

• LIMBAL CONTACT LENS WEAR IN EYES WITH OCULAR SURFACE SCARRING: The limbal CLs were able to be used for eyes with fornix shortening, conjunctivalization, and neovascularization of the cornea, and there was no need to fill the CL with saline or artificial tears. During limbal CL wear, a thin fluid layer existed beneath the CL (Figure 4) and the precorneal fluid layer exchanged at every blink (Supplemental Video, available at AJO.com).

• VISUAL ACUITY: Best-corrected visual acuity improved from 1.61 to 0.86 logMAR after 3 months of limbal CL use, and in 43 eyes (81.1%), the BCVA improvement was more than 0.2 logMAR (Figure 5). The BCVA

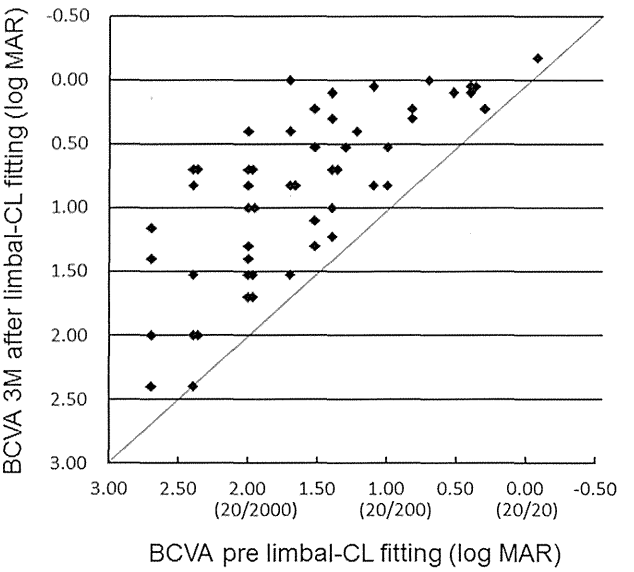

FIGURE 5. Scatterplot showing the change in best-corrected visual acuity (BCVA) measured in logarithm of the minimal angle of resolution (logMAR) units before and at after 3 months use of the limbal contact lens in 42 patients (53 eyes) with ocular sequelae resulting from Stevens-Johnson syndrome or toxic epidermal necrolysis. The diagonal line indicates the values at which the preoperative and postoperative visual acuity values were the same. Counting fingers, hand movements, and light perception were determined to be 0.004, 0.002, and 0.001, respectively.

improvement in groups 1, 2, and 3 was 0.95 logMAR, 0.82 logMAR, and 0.37 logMAR, respectively (Table 2). Mean BCVA after 3 months of CL use was 1.55 logMAR in group 1, the worst among the 3 groups. However, BCVA improvement was best in group 1. Of 29 cases in which the CL was fitted unilaterally, the CL was fitted in the eye with better VA in 26 cases and in the eye with worse VA in 3 cases. At the final examination, the eye fitted with the limbal CL was the eye with better VA in all 29 unilateral cases.

• VISUAL FUNCTION QUESTIONNAIRE: The mean NEI VFQ-25 composite score of the 11 subscores improved from 37.6 ± 16.0 to 58.4 ± 17.4 ($P = .000001$). Significant improvement was found in all 11 subscores, except for the score for driving ability (Table 3). Significant improvement was found not only in the vision-related subscores, but also in the behavioral subscores. It should be emphasized that the subscore for mental health (ie, patient well-being) was very low in group 1, but greatly improved after using the limbal CL.

Comparison of the subscores among the 3 groups revealed that the vision-related subscores most improved in group 3, except for the score for color vision. However, the subscores of general health most improved in group

TABLE 2. Comparison of the Change of Visual Acuity Among the 3 Groups Divided According to Best-Corrected Visual Acuity Before Limbal Contact Lens Fitting

		BCVA Before Limbal CL Fitting		
	Total	Group 1: BCVA Worse Than 20/2000 (logMAR >2), Average Grade	Group 2: BCVA 20/200 to 20/2000 (2 ≥ logMAR > 1), Average Grade	Group 3: BCVA 20/200 or Better (1 ≥ logMAR), Average Grade
No. of eyes	53	11	31	11
BCVA before limbal CL fitting (logMAR)	1.61	2.51	1.67	0.57
BCVA after 3 months of limbal CL use (logMAR)	0.86	1.55	0.85	0.20
BCVA improvement (logMAR)	0.75	0.95	0.82	0.37

BCVA = best-corrected visual acuity; CL = contact lens; logMAR = logarithm of the minimal angle of resolution.

1 (Table 4). Among the behavioral subscores, social functioning and dependence improved almost equally in the 3 groups. Both mental health and role difficulties (ie, role limitations) improved most in group 3, but the improvement of mental health in group 1 also was high.

• LIMBAL CONTACT LENS SIZE, BASE CURVE, AND PERIPHERAL DESIGN: Of the total 53 eyes, the diameter of the limbal CL was 14.0 mm in 45 eyes, 13.0 mm in 6 eyes, 12.5 mm in 1 eye, and 16 mm in 1 eye. The base curve of the lens ranged from 780 to 810 mm in 48 eyes (ie, 750 mm in 1 eye, 760 mm in 1 eye, 770 mm in 3 eyes, 780 mm in 18 eyes, 790 mm in 12 eyes, 800 mm in 7 eyes, and 810 mm in 11 eyes). The size of the optical zone was 8.0 mm in 2 eyes, 8.5 mm in 32 eyes, 9.0 mm in 17 eyes, and 9.5 mm in 2 eyes. The peripheral design was the flat-pattern type in 49 eyes and the tight-pattern type in 4 eyes.

Because of the highly irregular corneal surface in each patient, the corneal shape could not be evaluated by use of topography. To determine the CL size, base curve, and peripheral design, we first tested the CL fitting using the 790/0/14.0-8.5 flat-pattern type. Next, we changed and tested the CL, step by step, by evaluating the fluorescein staining pattern both at rest and during blinking. In the eyes with slight scarring of the ocular surface, the large optical zone CL was well fitted and the peripheral tight-pattern design was preferred.

• LENGTH OF TIME OF CONTACT LENS WEAR AND ADVERSE EVENTS: In 33 eyes, the limbal CL was used from morning into the evening, that is, more than 12 hours per day. In 3 eyes, the CL was used only during the part of the day when the patients left their house to go outside. In 3 eyes, the patients reported eye pain after several hours of CL wear; all 3 eyes had severe scarring of the upper fornix, and the symblepharon was asymmetrical between the upper and lower fornix. In 1 eye, a small epithelial erosion occurred, but healed within several days after the discontinuation of CL wear. No other complications or infections occurred as a result of CL wear. Seven patients lost their CL because of low VA, making it extremely difficult for them to find the CL by themselves.

DISCUSSION

THE OCULAR SEQUELAE RESULTING FROM SJS OR TEN CAN be devastating to a patient's vision, and the associated severe ocular discomfort is extremely serious and lasts throughout the patient's life. The improved VA and quality of life achieved through the use of the tear-exchangeable limbal CL are encouraging, because this CL has the potential of being a new treatment option that can provide better VA, improved ocular comfort, or both for patients with SJS or TEN.

It should be emphasized that before the initial use of this new CL, BCVA in 79% of the eyes (42 of the 53 eyes) was worse than 20/200 (groups 1 and 2). Moreover, BCVA in 21% of the eyes (11 of the 53 eyes) before CL use was worse than 20/2000, hand movements, or counting fingers (group 1). The mean change in BCVA was 0.95 logMAR, the greatest change being in group 1. Visual acuity improved immediately after the CL fitting, and the patients were surprised with the instant improvement. In fact, that improvement of VA allowed some of the patients to see their doctor's face for the first time.

With the use of this new CL, spontaneous exchange of tear fluids or artificial tears occurs during every blink. In contrast, with the use of scleral CLs (diameter, 16 to 23 mm), there is little or no exchange of tear fluids or artificial tears, and the CL must be cleaned every 4 to 6 hours. Our findings show that all-day wear of our new CL is possible, because there is no need to remove and clean the CL during that extended period.

In recent years, semiscleral CLs with a diameter of 15.0 to 18.0 mm were reported to offer the benefit of improving VA in eyes with severe dry eye or an irregular cornea.[38,39]

TABLE 3. Twenty-five-Item National Eye Institute Visual Function Questionnaire Results for the Patients With Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis Before and After 3 Months of Limbal Contact Lens Use

	Before CL Fitting	After CL Fitting	Mean Change	*P* Value[a]
Composite score 11				
Mean ± SD	37.6 ± 16.0	58.5 ± 17.4	20.8 ± 15.8	.000001
Median (range)	35.2 (8.4 to 69.4)	58.4 (23.2 to 92.7)	21.6 (–17.2 to 59.7)	
Composite score 7				
Mean ± SD	35.7 ± 16.0	58.4 ± 17.6	22.7 ± 17.6	.000001
Median (range)	35.1 (4.3 to 67)	57.2 (17.0 to 93.9)	20.7 (–17.4 to 67)	
Subscale scores				
General health				
Mean ± SD	47.4 ± 21.2	58.8 ± 15.1	11.4 ± 21.6	.006265
Median (range)	50 (0 to 100)	60 (5 to 85)	0 (–27.5 to 65)	
Vision-related subscales				
General vision				
Mean ± SD	32.6 ± 15.8	65.1 ± 20.3	32.6 ± 22.6	.000001
Median (range)	30 (0 to 75)	70 (0 to 100)	35 (–15 to 75)	
Near vision				
Mean ± SD	31.1 ± 17.0	53.1 ± 21.7	22 ± 19.9	.000007
Median (range)	29.2 (0 to 66.7)	54.2 (8.3 to 100)	22.5 (–16.7 to 66.7)	
Distance vision				
Mean ± SD	29.9 ± 17.2	53.4 ± 18.3	23.5 ± 18.7	.000003
Median (range)	33.3 (0 to 62.5)	50 (12.5 to 95)	25 (–12.5 to 60)	
Color vision				
Mean ± SD	62.9 ± 24.2	77.1 ± 21.0	14.3 ± 24.1	.003496
Median (range)	75 (0 to 100)	75 (0 to 100)	0 (–50 to 75)	
Peripheral vision				
Mean ± SD	33.1 ± 24.0	50.0 ± 23.9	16.9 ± 25.5	.000447
Median (range)	25 (0 to 100)	50 (0 to 100)	25 (–75 to 75)	
Ocular pain				
Mean ± SD	43.9 ± 29.9	65.7 ± 25.9	21.8 ± 24.7	.000061
Median (range)	50 (0 to 100)	75 (12.5 to 100)	12.5 (–25 to 87.5)	
Behavioral subscales				
Mental health				
Mean ± SD	28.9 ± 21.1	52.8 ± 22.8	23.9 ± 21.5	.000003
Median (range)	25 (0 to 80)	55 (10 to 95)	20 (–15 to 75)	
Social function				
Mean ± SD	51.8 ± 16.8	66.9 ± 17.5	15.1 ± 20.9	.000661
Median (range)	50 (25 to 91.7)	66.7 (33.3 to 100)	16.7 (–25.0 to 58.3)	
Role limitation				
Mean ± SD	36.3 ± 22.6	57.4 ± 20.9	21.2 ± 20.6	.000009
Median (range)	37.5 (0 to 81.3)	56.3 (0 to 100)	18.8 (–18.8 to 68.8)	
Dependency				
Mean ± SD	39.5 ± 25.6	60.4 ± 22.4	20.9 ± 21.7	.000009
Median (range)	43.8 (0 to 87.5)	62.5 (12.5 to 100)	18.8 (–18.8 to 93.8)	
Ability to drive				
Driving				
Mean ± SD	6.1 ± 18.7	14.6 ± 29.8	9.9 ± 20.5	.278517
Median (range)	0 (0 to 75)	0 (0 to 100)	0 (0 to 75)	

CL = contact lens; SD = standard deviation.
[a]Wilcoxon signed-rank test.

The limbal CL presented in this study may seem to be similar to a large-diameter rigid gas permeable CL or a semiscleral CL. However, the chief difference between our new CL and a semiscleral or large-diameter CL is the entrapment of the fluid reservoir beneath the flange that extends beyond the limbus when using this CL. To bring the tear under the CL automatically, the CL design includes a multicurve zone at the periphery of the CL, thus

TABLE 4. Comparison of the Change of the 25-Item National Eye Institute Visual Function Questionnaire Scores Before and After 3 Months of Limbal Contact Lens Use among the 3 Groups Divided According to Best-Corrected Visual Acuity before Limbal Contact Lens Fitting

	Total	Group 1: BCVA Worse Than 20/2000 (logMAR > 2), Average Grade	Group 2: BCVA 20/200 to 20/2000 (2 ≥ logMAR > 1), Average Grade	Group 3: BCVA 20/200 or Better (1 ≥ logMAR), Average Grade
No. of cases	35	8	18	9
Composite score 11	20.8	18.1	20.2	24.5
Composite score 7	22.7	20.8	21.5	26.9
Subscale scores				
General health	11.4	13.8	12.6	6.9
Vision-related subscales				
General vision	32.6	26.3	30.8	41.7
Near vision	22.0	19.6	19.5	29.1
Distance vision	23.5	23.8	22.2	25.8
Color vision	14.3	9.4	18.1	11.1
Peripheral vision	16.9	12.5	17.6	19.4
Ocular pain	21.8	21.9	20.1	25.0
Behavioral Subscales				
Mental health	23.9	25.6	19.5	31.1
Social function	15.1	14.6	16.2	13.4
Role limitation	21.2	18.0	20.1	26.2
Dependency	20.9	18.0	22.2	20.8
Ability to drive				
Driving	9.9	0.0	2.1	28.3

BCVA = best-corrected visual acuity; logMAR = logarithm of the minimal angle of resolution.

establishing a thin tear layer on the entire corneal surface that can bring relief to the patients with severe ocular discomfort.

Our new CL comprises an 8.5- or 9.0-mm diameter central zone and a peripheral zone that lies on the corneal and conjunctival limbus. During the lens design process, we found that in the eyes with severe cicatrization of the ocular surface, the shape of the sclera beyond the limbus is flatter than that of normal eyes. Therefore, the peripheral zone in our limbal CL was designed to be flatter than the central optical zone, and it incorporates a projecting multicurve edge design that is like the brim of a hat. Although our limbal CL with an 8.5-mm diameter central zone was well fitted in the severely cicatrized eyes in comparison with the moderately affected eyes, the CL with a 9.0-mm diameter central zone was well fitted in moderately damaged eyes or in the eyes without fornix shortening. The peripheral design with the flat-pattern type was well fitted in the moderate to severe cicatrized eyes. In contrast, the peripheral design with the tight-pattern type was well-fitted in the eyes with slight or no cicatrized eyes.

As reported previously, the quality of life in SJS or TEN patients is worse than that in the patients with Sjögren syndrome.[35,40] Use of our limbal CL not only increased the patients' VA, but also improved their general health and mental health. In fact, even the end-stage blind patients (group 1) experienced improved vision and general health. Moreover, because of the decrease of tear evaporation, eye pain also decreased during CL wear. The use of scleral CLs reportedly reduces symptoms related to severe dry eye,[31,32] and our findings show that using our new limbal CLs also reduces those same symptoms.

It should be noted that COMET is reportedly a reliable option for obtaining improved vision in eyes with end-stage SJS or TEN.[24] However, the damage in the eyes treated by COMET in that study was more severe than in the eyes enrolled in this present study. In this study, 11 cases used this CL after ocular surface reconstruction using the COMET technique. These patients were able to obtain improved vision by COMET alone, yet use of the limbal CL enhanced that improvement of vision. Thus, the use of this CL alone, or the 2-step treatment of COMET and limbal CL use, are safe and reliable treatment methods for ocular sequelae resulting from SJS or TEN. In conclusion, the findings of this study show that our new tear-exchangeable, limbal CL increases VA and also increases general health and mental health in SJS or TEN patients, especially those with end-stage blindness.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and the following were reported. Naoki Yamauchi and Soshun Maeda are employees of Sun Contact Lens Co., Ltd., Kyoto, Japan. Supported in part by a Research Grant from the New Energy and Industrial Technology Development Organization (NEDO) of the Japanese Ministry of Economy, Trade and Industry; a Grant-in-Aid for Scientific Research from the Japanese Ministry of Health, Labor and Welfare; and a Research Grant from the Japanese Ministry of Education, Culture, Sports, Science and Technology (J132004135). Involved in Conception and design of study (C.S., S.K.); Data collection (C.S., N.Y., S.M.); Analysis and interpretation of data (C.S.); Preparation of manuscript (C.S., N.Y., S.K.); Critical revision of manuscript (C.S.); and Final approval of manuscript (C.S., N.Y., S.M., S.K.). The authors thank Dr Aoi Komuro of Kyoto Prefectural University of Medicine for expert evaluation of tear exchange, Saeko Miyazaki of Kyoto Prefectural University of Medicine for administering the direct patient VFQ interviews and data collection, and Yoshimi Suzukamo of Tohoku University for assistance with scoring of the VFQ interviews, and give special thanks to John Bush of Kyoto Prefectural University of Medicine for reviewing the manuscript.

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指定番号（２６機）第２７号

希少疾病用医療機器指定書

平成26年11月４日付けで申請のあった次の医療機器を、薬事法（昭和35年法律第145号）第77条の２第１項の規定に基づき、希少疾病用医療機器として指定する。

医療機器の名称	輪部支持型ハードコンタクトレンズCS-100
予定される使用目的、効能又は効果	重症多形滲出性紅斑（スティーブンス・ジョンソン症候群、中毒性表皮壊死症）の眼後遺症の視力補正及び症状緩和
氏名又は名称	株式会社サンコンタクトレンズ

平成２６年１２月１９日

厚生労働大臣　塩崎　恭久

平成26 年度厚生労働科学特別研究事業 進捗管理班成果報告会

- アカデミアにおけるイノベーション創出の現状と展望 -

日 時： 2015 年3 月13 日 (金) 10:00 ~ 17:30 (開場9:00)

会 場： 東京コンベンションホール

東京都中央区京橋三丁目1 - 1 東京スクエアガーデン5F

発表課題： 全126 課題 (口頭発表 : 36 課題、ポスター掲示 : 90 課題)

重症多形滲出性紅斑の眼後遺症に対する輪部支持型ハードコンタクトレンズの臨床試験

Clinical Trial of Limbal Rigid Contact Lens in the Patients with Ocular Sequelae Due to Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis.

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所属： 京都府立医科大学大学院 視覚機能再生外科学
役職： 講師
専門領域：難治性角結膜疾患

Dr. Chie Sotozono graduated from the Kyoto Prefectural University of Medicine, Kyoto, Japan in 1986. At present, Dr. Sotozono is an Assistant Professor in the Department of Ophthalmology at Kyoto Prefectural University of Medicine, and specializes in clinical research and severe ocular surface disorders.

概要：

重症多型滲出性紅斑（Stevens-Johnson 症候群および中毒性表皮壊死症）は、突然の高熱とともに皮膚・粘膜に発疹とびらんを生ずる全身性の皮膚粘膜疾患である。致死率が高く急性期には全身管理が主体となるが、救命しても高度の視力障害とドライアイが後遺症となり、社会復帰が困難となる。高度視力障害には、角膜混濁に加えて眼表面全体に及ぶ不正乱視、癒着が関与する。そこで我々は、独自にデザインしたハードコンタクトレンズ（輪部支持 CL）を開発し、本疾患患者 42 例 53 眼を対象に先行臨床研究を実施、著しい視力改善と QOL 改善を認めた。医薬品機構の薬事戦略相談を重ねた結果、薬事承認を目指して医師主導型治験を実施することとした。平成 25 年 10 月にプロジェクトチームを発足、研究計画書及び概要書を作成、平成 26 年 1 月に対面助言を実施し、京都府立医大と京都大学の二施設治験、目標症例数を 10 例、観察期間を 13 週と決定した。同年 4 月に治験届を提出、6 月 4 日に第 1 症例を登録、12 月 16 日に最終症例の観察を終了した。治験を中止した症例はなく、重篤な有害事象を生じた症例もなかった。平成 27 年 1 月にデータ固定を行い、治験の結果を解析中である。治験実施と並行して、京都府立医科大学の臨床研究体制の整備に向けて、支援部門の構築とその活動を開始した。また希少疾病用医療機器の申請を行い、平成 26 年 12 月に承認を得た。平成 27 年春に本医療機器を薬事申請する予定である。

Stevens-Johnson syndrome (SJS), and its severe variant, toxic epidermal necrolysis (TEN), are acute, life-threatening diseases of the skin and mucous membranes. The motality rate at acute stage is high, but even if patient's life is saved, visual impairment and ocular discomfort continue throughout the life. Recently, we developed a new type of rigid contact lens (limbal CL) originally designed for SJS/TEN-associated ocular sequelae. In our previous study to evaluate the effects of limbal CL, marked improvement of visual acuity and quality of life was obtained in 42 SJS/TEN patients. After the consultation to PMDA, the details of clinical trial were determined. We started clinical trial of limbal CL in June 2014. Ten cases were enrolled; 8 cases in Kyoto Prefectural University of Medicine and 2 cases in Kyoto University. Thirteen weeks follow-up observations were done in all cases. It's expected to get the approval of manufacture and sale of this medical equipment in future.

重症多形滲出性紅斑の眼後遺症に対する輪部支持型ハードコンタクトレンズの臨床試験

Clinical Trial of Limbal Rigid Contact Lens in the Patients with Ocular Sequelae Due to Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis.

外園千恵　京都府立医科大学大学院　視覚機能再生外科学

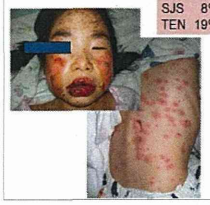
重症多形滲出性紅斑

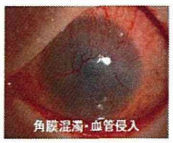
（SJS: Stevens-Johnson症候群およびTEN:中毒性表皮壊死症）

- 人口100万人あたり、1年に2-6名程度の発症
- 突然に高熱、全身の皮膚・粘膜に発疹・水疱

急性期　致死率 SJS 8% TEN 19%　　慢性期

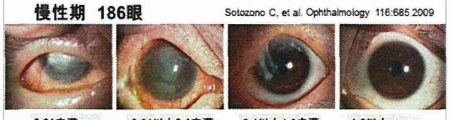
✓ 視覚障害・高度ドライアイ
✓ 若年者が多い





慢性期　186眼

Sotozono C, et al. Ophthalmology 116:685 2009



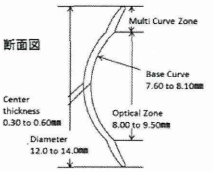
0.01未満	0.01以上0.1未満	0.1以上1.0未満	1.0以上
44眼 (23.7%)	53 眼 (28.5%)	55 眼 (29.6%)	34 眼 (18.3%)

52.2%

角膜混濁による失明

癒着・乾燥・表面不整

✓ 角膜を覆う
✓ レンズ下で涙液交換



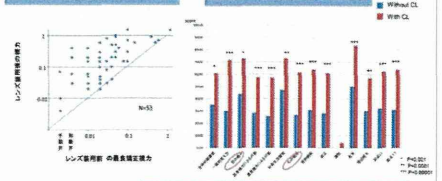
先行臨床研究

NEDO　平成22－24年度
視覚障害介護対象者の社会生活向上のためのスクレラルレンズの開発

結果
- 重症多形滲出性紅斑 53眼中42眼(79%)が装用前視力0.1未満
- 著明な視力改善、QOL改善(眼痛の軽減、心の健康)
- 有害事象：角膜びらん(2眼のみ、速やかに治癒)

有用かつ安全

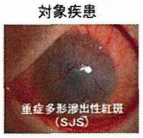
主要エンドポイント：視力の改善　　副次エンドポイント：QOLの改善



患者さんの要望　生涯使い続けたい
紛失、破損に備えて、スペアを購入したい

目標　医師主導治験を実施、医療機器として承認

対象疾患



試験物の名称

プロトコール骨子

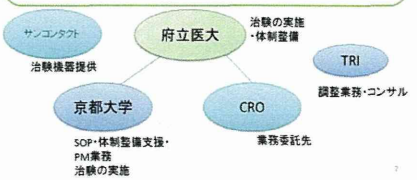
実施医療機関	京都府立医科大学 +京都大学
対象	重症多形滲出性紅斑
目標症例数	10例
エンドポイント	1）視力改善 2）QOL改善

概要

治験課題名	重症多形滲出性紅斑の眼後遺症に対する輪部支持型ハードコンタクトレンズCS-100の臨床試験
治験の目的	重症多形滲出性紅斑の眼後症を対象として輪部支持型ハードコンタクトレンズCS-100の有効性及び安全性を確認する
治験デザイン	非対照、オープンラベル試験
対象	重症多形滲出性紅斑の眼後遺症を有する患者
目標被験者数	10 例
治験期間	同意取得から装用開始後13週間

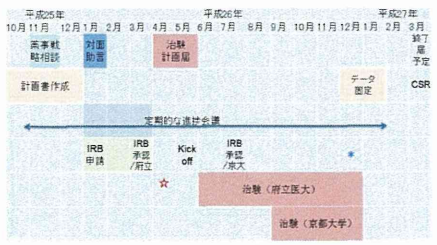
実施体制

研究代表者・調整医師：外園（府立医大）
調整事務局：今井（府立医大　医療フロンティア展開学）
2名（CRC実務担当＋事務局業務担当）
治験責任医師：外園（府立医大）＋荻野（京大病院）
分担研究者：上田、今井（府立医大）、角（京大）



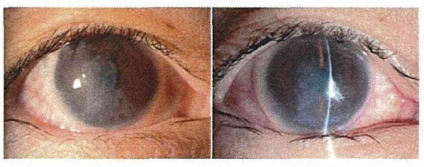
採択後の経緯

・医師主導治験届提出　（平成26年4月8日）
・症例登録開始(FPI)　（平成26年6月4日）
・治験終了(LPO)　（平成26年12月16日）



代表症例

35歳女性



開始前　最良矯正視力 0.05　　終了時　最良矯正視力 0.5

重症多型滲出性紅斑眼障害の克服に向けた新規医療器具の開発研究班

外園千恵	京都府立医科大学大学院　視覚機能再生外科学	講師
上田真由美	同志社大学　生命医科学部	准教授
角　栄里子	京大病院　臨床研究総合センター　早期臨床試験部	助　教
羽室　淳爾	京都府立医科大学	特任教授
寺良向　聡	京都府立医科大学大学院　生物統計学	教　授
今井浩二郎	京都府立医科大学大学院・医療フロンティア展開学	講　師
荻野　顕	京都大学　眼科学	助　教
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