December 4, 2019

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

Report on the Deliberation Results

Classification	Instrument & Apparatus 71, Eyewear for Vision Correction
Term Name	Laser retinal scanning type eyewear
Brand Name	RETISSA Medical
Applicant	QD Laser, Inc.
Date of Application	February 21, 2019 (Application for marketing approval)

Results of Deliberation

In its meeting held on December 4, 2019, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

Review Report

November 12, 2019
Pharmaceuticals and Medical Devices Agency

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

Classification	Instrument & Apparatus 71, Eyewear for Vision Correction
Term Name	Laser retinal scanning type eyewear (Planned to be newly created)
Brand Name	RETISSA Medical
Applicant	QD Laser, Inc.
Date of Application	February 21, 2019
Items Warranting Special Mention	None
Reviewing Office	Office of Medical Devices I

Review Results

November 12, 2019

Classification	Instrument & Apparatus 71, Eyewear for Vision Correction
Term Name	Laser retinal scanning type eyewear (Planned to be newly created)
Brand Name	RETISSA Medical
Applicant	QD Laser, Inc.
Date of Application	February 21, 2019

Results of Review

RETISSA Medical is a laser projector eyewear intended to correct visual acuity in patients with irregular astigmatism. RETISSA Medical has a camera built into the frame of the image projection part of the eyewear. An object photographed by this camera is converted to a laser beam composed of red, green, and blue (RGB) lights in the visible light spectrum (red light, peak wavelength 634 nm, wavelength range 631-641 nm; green light, peak wavelength 521 nm, wavelength range 513-523 nm; blue light, peak wavelength 466 nm, wavelength range 460-470 nm) (output 0.316 μW + 15%/-30%). Then, the RGB laser beam converted from the image is projected to the retina.

The applicant submitted non-clinical data supporting the electrical safety and electromagnetic compatibility, biological safety, radiation safety, mechanical safety, stability and durability, performance, and directions for use of RETISSA Medical. The safety of the laser was evaluated mainly based on radiation safety. The data indicated that the laser of RETISSA Medical is a Class 1 laser according to International Electrotechnical Commission (IEC) 60825-1, a Class 1 laser according to Japanese Industrial Standards (JIS) C 6802, and a Class I laser according to Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) 1040.10. No particular problem with the safety of the laser was shown.

The applicant submitted the clinical data from a clinical study involving 16 eyes of 15 patients at 2 study sites in Japan. The efficacy of RETISSA Medical was evaluated based on the change from baseline in the logarithm of the Minimum Angle of Resolution (logMAR) visual acuity. A comparison of the change from baseline in logMAR between the RETISSA group and the spectacle group showed a statistically significant difference of -0.395 in favor of the RETISSA group. The safety of RETISSA Medical was also evaluated. Two adverse events reported were mild conjunctival hyperaemia and mild nasopharyngitis. RETISSA Medical had a clinically acceptable safety profile.

As a result of overall evaluation of the submitted data based on the conclusion of the Expert Discussion, PMDA concluded that there was no particular problem with the efficacy and safety of RETISSA Medical.

As a result of its review, PMDA has concluded that RETISSA Medical may be approved for the intended use shown below and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use

RETISSA Medical is intended to correct the visual acuity of patients whose vision is affected by irregular astigmatism (whose vision cannot be corrected sufficiently by conventional glasses or contact lenses).

Review Report

November 12, 2019

Product for Review

Classification	Instrument & Apparatus 71, Eyewear for Vision Correction
Term Name	Laser retinal scanning type eyewear (Planned to be newly created)
Brand Name	RETISSA Medical
Applicant	QD Laser, Inc.
Date of Application	February 21, 2019
Proposed Intended Use	RETISSA Medical corrects low visual acuity caused by anterior eye diseases (mainly irregular astigmatism) in patients with vision disorders.

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List of Abbreviations

AC	Alternating Current
CFR	Code of Federal Regulations
CPM	Characters per Minute
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
fps	Frame per Second
IEC	International Electrotechnical Commission
IReST	International Reading Speed Texts
ISO	International Organization for Standardization
JIS	Japanese Industrial Standards
logMAR	Logarithm of the Minimum Angle of Resolution
MNREAD-J	Minnesota READ-Japanese
OCT	Optical Coherence Tomography
PPS	Per Protocol Set
PT	Point
QOL	Quality of Life
RGB	Red, Green and Blue
UMIN	University Hospital Medical Information Network
WHO	World Health Organization

I. Product Overview

RETISSA Medical is a medical device that corrects the visual acuity of patients with irregular astigmatism. RETISSA Medical was developed as the medical device with a Maxwellian view system that delivers a laser beam to the center of the pupil and thereby focuses images on the retina without depending on the refractive power of the cornea or lens. RETISSA Medical has a camera built into the image projection part of the eyewear. An object photographed by this camera is converted to a red, green, and blue (RGB) laser beam (laser output 0.316 μW + 15%/-30%) consisting of a visible red laser (peak wavelength 634 nm, wavelength range 631-641 nm), a visible green laser (peak wavelength 521 nm, wavelength range 513-523 nm), and a visible blue laser (peak wavelength 466 nm, wavelength range 460-470 nm) (Figures 1 and 2). RETISSA Medical comes in 4 types, 2 frame sizes (width) (S or M) and 2 different locations of the optical part (left or right) (Figure 3). A laser beam delivered from the optical part of the image projection part of the eyewear is delivered to the retina via a light reflector (Figure 4). To use RETISSA Medical, first the patient activates the control box and moves the image projection part of the eyewear close to the eye while looking at the dot on the reflector (Figure 5). With the zoom button, the magnification can be changed to 0.5, 1.0, or 2.0.

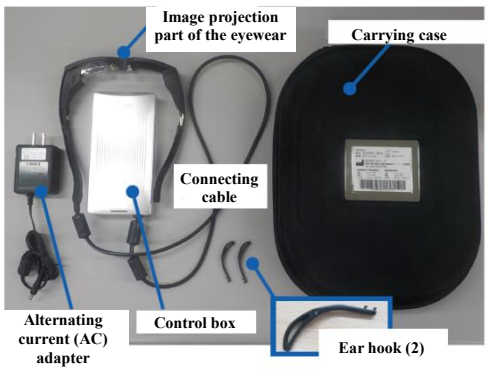


Figure 1. Overall view of RETISSA Medical

Size of control box: 160 mm × 80 mm × 31 mm

Figure 2. Exterior appearance of RETISSA Medical

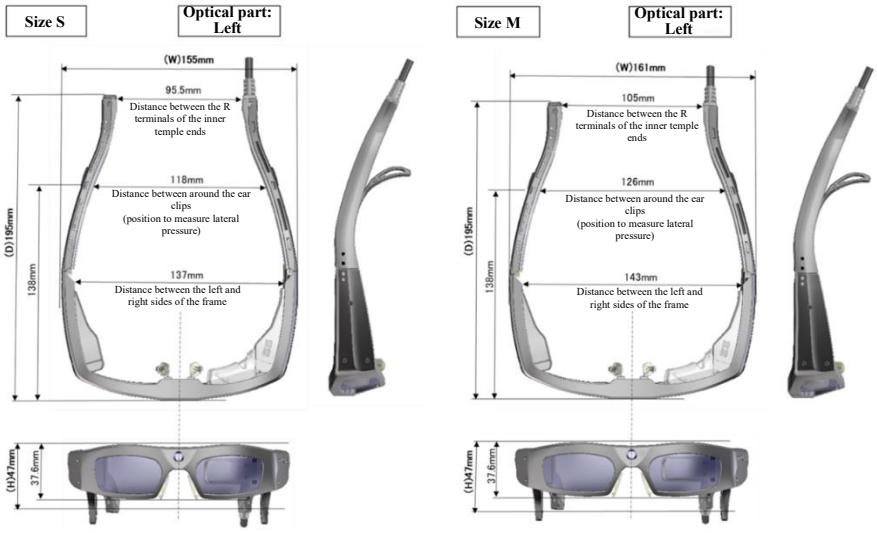


Figure 3. Appearance of the image projection part of the eyewear (optical part, left)

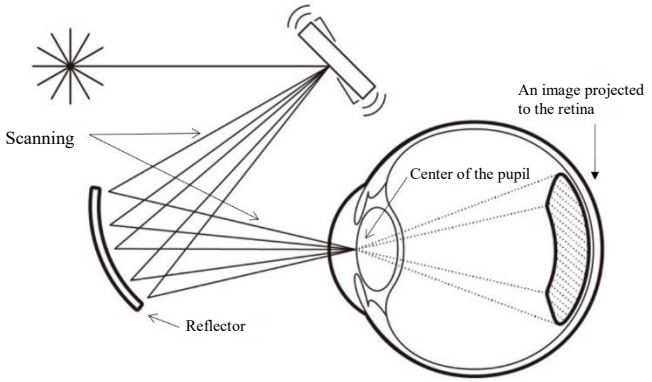


Figure 4. Schematic diagram of retinal scanning

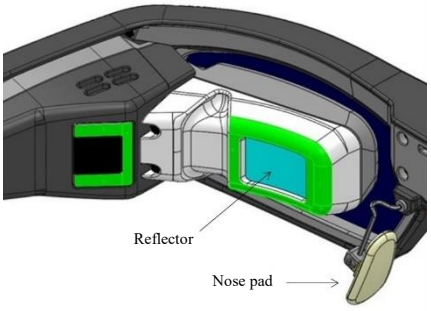


Figure 5. Enlarged view of optical part

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

The data submitted for the present application by the applicant 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 RETISSA Medical declared that they did not fall under Item 5 of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA administrative Rule No. 8/20 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

Low visual acuity due to refraction errors, such as myopia, hypermetropia, and astigmatism, can be corrected by wearing eyeglasses or contact lenses. Optical correction with eyeglasses or contact lenses enables images to be focused on the retina. Myopia, in which images are focused in front of the retina, can be corrected with a concave lens (spherical or non-spherical). Hypermetropia, in which images are focused behind the retina, can be corrected with a convex lens (spherical or non-spherical). Regular astigmatism, in which images are focused at different points between vertical and horizontal meridians, can be corrected with a cylindrical lens. However, a cylindrical lens does not fully correct low visual acuity due to irregular astigmatism[1)] caused primarily by corneal diseases because of an irregular refracting surface, which is characteristic to irregular astigmatism.

Causes of irregular astigmatism include keratoconus, pellucid marginal corneal degeneration, and pterygium.[1)] Approximately 1 in 2,000 people has keratoconus.[2)] The number of patients with pellucid marginal corneal degeneration is estimated to be approximately one-twentieth to one-fortieth of that of keratoconus patients.[3)] For example, poor vision due to keratoconus characterized by thinning or deformation of the corneal center can be corrected with eyeglasses or soft contact lenses when the severity of corneal herniation is mild. In advanced cases, however, only a hard contact lens can correct visual acuity. Patients with a severe corneal deformation may feel discomfort or pain when they wear a hard contact lens because of mechanical friction. Wearing a hard contact lens for a long period of time can be challenging for them. In addition, hard contact lenses may fall off when their shapes do not match the corneal shapes of patients. More advanced keratoconus requires corneal transplant.[2)]

Currently, Menicon ROSE K-T (marketing authorization holder, Menicon Co., Ltd.; Approval number 22900BZX00397000) is the only hard contact lens approved for the indication of keratoconus.

Patients who fail to achieve enough visual acuity correction by the aforementioned methods or cannot use or wear hard contact lenses use an optical aid (e.g., magnifying glass and magnifier reading aid) to maintain or improve their quality of life (QOL).[4)]

RETISSA Medical is a medical device that uses a Maxwellian view system to correct visual acuity. Maxwellian view systems deliver a laser beam to the center of the pupil and thereby focus images on the retina without depending on the refractive power of the cornea or lens (Figure 6). RETISSA Medical was developed on the basis of this principle to correct visual acuity without being affected by a corneal or lens disease causing irregular astigmatism.

RETISSA Medical corrects visual acuity in patients who:

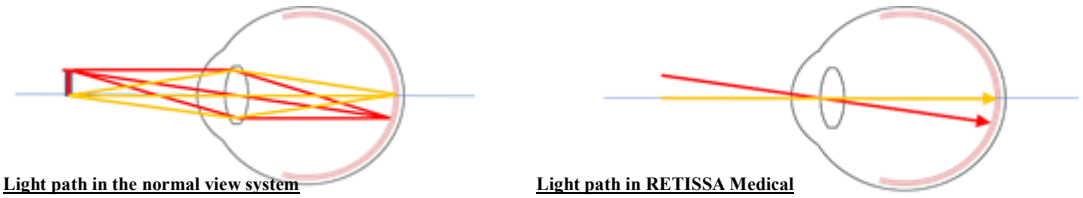
(a) Have difficulty in using a hard contact lens because of discomfort or pain, or

(b) Have a cornea that does not match the shape of a hard contact lens, causing the contact lens to fall.

RETISSA Medical was selected for "Establishment of Infrastructure for Applications of Most Advanced Visible Laser Diode Devices" in Clean Device Promotion Project FY 2014 to 2016 and for "Development of Retinal Imaging Laser Eye Wear for Optical Support" in Development of Practical Applications of Assistive Devices for Problem Solving Support Project FY 2015 by New Energy and Industrial Technology Development Organization. In these projects, the practical development of RETISSA Medical was initiated.

Figure 6. Maxwellian view system

The normal view system focuses images on the retina using the refractive power of the cornea and lens (left figure). The ciliary zonules (zonules) control the lens thickness to adjust the refractive power in order to focus images on the retina. On the other hand, Maxwellian view systems[5)] are based on the nature of light that a light beam passing through the lens center does not refract. Maxwellian view systems deliver a light beam to the center of the pupil to create a light path passing through the lens center, thereby focusing images on the retina without depending on the refractive power of the cornea or lens, (right figure).



Light path in the normal view system
Dependent on the refractive power of the eye

Light path in RETISSA Medical
Independent of the refractive power of the eye

1.(2) Use in foreign countries

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

RETISSA Medical is not approved or licensed in any foreign countries.

1.(3) Malfunctions and adverse events in foreign countries

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

RETISSA Medical has not been used in any foreign countries.

2. Design and Development

2.(1) Physicochemical properties

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

The applicant did not submit the data on the physicochemical properties of RETISSA Medical because they are included in the Sections "2.(4) Radiation safety," "2.(5) Mechanical safety," "2.(6) Stability and durability," and "2.(7) Performance" later discussed.

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

PMDA concluded that there was no particular problem with not submitting physicochemical data.

2.(2) Electrical safety and electromagnetic compatibility

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

To support the electrical safety and electromagnetic compatibility of RETISSA Medical, the applicant submitted data demonstrating that RETISSA Medical meets the international standard that specifies general requirements for basic safety and essential performance of medical electrical equipment (IEC 60601-1:2005 and Amendment 1:2012), and the international standard that specifies general requirements for the basic safety and essential performance of the medical electrical equipment (electromagnetic compatibility) (IEC 60601-1-2:2014). The test results showed that RETISSA Medical conformed to both standards, assuring its electrical safety and electromagnetic compatibility.

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

PMDA reviewed the electrical safety and electromagnetic compatibility data submitted, and concluded that there was no particular problem with these properties of RETISSA Medical.

2.(3) Biological safety

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

A study was conducted in accordance with the international standard on the biological evaluation of medical devices (International Organization for Standardization [ISO] 10993-1:2009) to evaluate the biological safety of the eyewear frame of the image projection part, which does not directly or indirectly come in contact with blood, body fluid, etc., but directly comes in contact with the skin. The applicant submitted the results of cytotoxicity, sensitization, and local tolerance studies of RETISSA Medical. No study showed any particular problem with RETISSA Medical, assuring its biological safety.

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

PMDA reviewed the biological safety data submitted and concluded that there was no particular problem with the biological safety of RETISSA Medical.

2.(4) Radiation safety

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

RETISSA Medical delivers a laser beam, which is non-ionizing radiation, through the center of the pupil. The laser beam passes through the optic media and reaches the retina. A study was conducted in accordance with the international standard on the safety of laser products (IEC 60825-1:2007) to evaluate the safety of the laser beam delivered by RETISSA Medical. RETISSA Medical with a laser output of 0.316 μW + 15%/-30% is classified as a Class 1 laser product (emission limit, red light 390 μW, green light 390 μW, blue light 78 μW). Class 1 laser products are safe during use, including long-term direct intrabeam viewing.

RETISSA Medical also meets the upper emission limit (0.39 μW) of Class I lasers, which are not considered dangerous, in the US FDA standard on the performance of light emitting products (21CFR1040.10).

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

PMDA reviewed the radiation safety data submitted and concluded that there was no particular problem with the radiation safety of RETISSA Medical, for the following reasons:

(a) The laser of RETISSA Medical is a Class 1 laser according to IEC 60825-1 and JIS C 6802. Such Class 1 lasers are safe during use, including long-term direct intrabeam viewing.
(b) The laser of RETISSA Medical meets the upper limit (0.39 μW) of Class I lasers according to FDA 21CFR1040.10. Such Class I lasers are not considered dangerous and do not pose a chronic hazard unlike other class lasers.
(c) Products having the same laser output as RETISSA Medical have already been used as consumer products.

2.(5) Mechanical safety

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

RETISSA Medical was evaluated for mechanical safety in accordance with the international standards (IEC 60601-1:2005 and Amendment 1:2012) described in the Section "2.(2) Electrical safety and electromagnetic compatibility." The applicant submitted data showing the conformity of RETISSA Medical to the international standard that specifies the general requirements for basic safety and essential performance of medical electrical equipment and medical electrical systems used in the home healthcare environment (IEC 60601-1-11:2015). The applicant also submitted data showing the conformity of RETISSA Medical to the international standard that specifies general requirements, including those for thermal hazards and mechanical hazards, applicable to ophthalmic instruments (ISO 15004-1:2006). The data assured the mechanical safety of RETISSA Medical.

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

PMDA reviewed the mechanical safety data submitted and concluded that there was no particular problem with the mechanical safety of RETISSA Medical.

2.(6) Stability and durability

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

The electrical parts of the control box and the image projection part of the eyewear have no specified shelf life because these parts do not require specific storage conditions to maintain their quality or prevent their quality loss over time. The raw materials of the image projection part that comes in contact with the patient's skin were examined for the degradation character of the resin. The applicant did not submit stability data for setting a shelf life in accordance with the "Handling of stability studies related to the determination of the shelf life in the Application for Approvals (Certifications) for Marketing Medical Devices" PFSB/ELD/OMDE Notification No. 1227-5 dated December 27, 2012, issued by the Director of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare. Instead, the applicant submitted a self-declaration stating that the shelf life of RETISSA Medical was determined based on the results of necessary stability studies.

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

PMDA concluded that there was no particular problem with not submitting stability and durability data.

2.(7) Performance

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

The applicant submitted performance data from the studies of (a) laser output, (b) white balance, (c) viewing angle, and (d) projection resolution and camera signal resolution.

(a) The laser beam of RETISSA Medical is composed of laser lights of red, green, and blue wavelengths. The maximum output from each color light (100% emission) results in white light. The maximum laser output (i.e., when white light is emitted) of RETISSA Medical is 0.316 μW + 15%/-30%, which met the requirement for Class I lasers according to FDA 21CFR1040.10.

(b) RETISSA Medical has a white point at 0.33 ± 0.08 on the chromaticity diagram.

(c) The preceding research demonstrated that subjects felt the projected image was too small at a viewing angle of ≤20° and had a feeling of being pressed at a viewing angle of ≥30°. On the basis of these results, the horizontal visual angle of 26° with an aspect ratio of 16:9 was selected.

(d) The projection resolution and camera signal resolution were determined to ensure that images corresponding to a decimal visual acuity of 0.4 to 0.5 are projected on the retina based on the World Health Organization (WHO)'s definition of low vision (best corrected decimal visual acuity, ≥0.05 and <0.3)[6]. The angle of 2 points the eyes can recognize is called visual angle (arc-minute). Its reciprocal is decimal visual acuity. The decimal visual acuity of 0.5, the target of RETISSA Medical, corresponds to the visual angle of 2.0' (= 1/0.5). The horizontal visual angle of 26°, which is a specification for RETISSA Medical, is equal to 1,560' (= 26 × 60). Because (a) a horizontal resolution of ≥780 dots (= 1560/2.0) is required to obtain this horizontal visual angle of 1,560' and (b) the aspect ratio is 16:9, the applicant selected the horizontal resolution of

1280 dots, vertical resolution of 720 lines, and frame rate of 60 frame per second (fps) for RETISSA Medical.

The test results showed that RETISSA Medical conformed to these specification limits, assuring its performance.

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

PMDA reviewed the performance data submitted and concluded that there was no particular problem with the performance of RETISSA Medical.

2.(8) Directions for use

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

For the directions for use of RETISSA Medical, conformity with the international standards on usability (IEC 62366:2007 and Amendment 1:2014) was evaluated along with the international standards (IEC 60601-1:2005 and Amendment 1:2012) described in the Section "2.(2) Electrical safety and electromagnetic compatibility." The results assured the directions for use of RETISSA Medial.

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

PMDA concluded that there was no particular problem with the data on the directions for use of RETISSA Medical and that the directions for use would be reviewed based on review results in Section "6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare."

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

The applicant 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 (MHLW Ministerial Announcement No. 122, 2005) (hereinafter, referred to as "Essential Principles"). The applicant also submitted data indicating the conformity of RETISSA Medical to the international standard that defines the life cycle process for medical device software (IEC 62304:2006).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of RETISSA Medical to the Essential Principles.

(a) Article 1 specifies 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). PMDA's conclusion on the conformity to the Article 1 is shown below.

As explained later in Section "6.B.(4).(a) Information to be provided to ensure proper use (contents of the instructions for use)," it is critical to evaluate the condition of the optic media, which is a pass for the laser light, and the function of the retina, where the laser light is projected, to assure the efficacy of RETISSA Medical. Therefore patients must be examined by an ophthalmologist for the condition of the optic media and the function of the retina, to appropriately determine their eligibility for the treatment with RETISSA Medical. PMDA instructed the applicant to include this information in the instructions for use and the applicant agreed.

(b) Article 3 includes the requirement that medical devices shall achieve the intended performance. PMDA's conclusion on the conformity to the Article 3 is shown below.

As explained later in Section "6.B.(1).(b) Disease for which RETISSA Medical is indicated," the target disease in the proposed intended use of RETISSA Medical is "Anterior eye diseases (mainly irregular astigmatism)." The clinical study submitted for the present application (hereinafter referred to as "the clinical study") enrolled and evaluated only patients with keratoconus; the efficacy and safety of RETISSA Medical in patients with other anterior eye diseases have not been evaluated. Taking account of comments raised in the Expert Discussion, PMDA concluded that the efficacy of RETISSA Medical in patients with irregular astigmatism with an irregular refracting surface can be evaluated on the basis of efficacy data from patients with keratoconus, who have an irregular refracting surface due to corneal thinning or deformation. PMDA instructed the applicant to change the proposed intended use from "Anterior eye diseases (mainly irregular astigmatism)" to "Irregular astigmatism," and the applicant agreed. In the clinical study, fundoscopy and optical coherence tomography (OCT) conducted in patients with keratoconus showed no retinal disorder (see Section "6.B.(2) Appropriateness of safety evaluation of RETISSA Medical,"). Since the clinical study enrolled patients with keratoconus and did not enroll patients with retinal disorder, the effect of laser irradiation in patients with retinal disease was not investigated. RETISSA Medical is a medical device that delivers a laser beam to the retina. It should be assumed that patients with retinal disease might consider the use of RETISSA Medical in clinical practice, although RETISSA Medical is indicated for irregular astigmatism. Taking account of comments raised in the Expert Discussion, PMDA instructed the applicant to inform users, via the instructions for use, that the safety of RETISSA Medical has not been established in patients with retinal disease because this patient population has not been exposed to laser radiation from RETISSA Medical. The applicant agreed.

(c) Article 17 defines requirements for information provision to users using instructions for use, etc. PMDA's conclusion on the conformity to the Article 17 is shown below.

As explained in Section "6.B.(2) Appropriateness of safety evaluation of RETISSA Medical," the effect of laser irradiation in patients with retinal disease has not been evaluated. The retinal function should be examined prior to the use of RETISSA Medical to prevent unnecessary laser irradiation in patients with retinal disease, who are not expected to respond to this therapy. If patients with low visual acuity of unidentified cause use RETISSA Medical without undergoing

an examination by an ophthalmologist, they may suffer a delay in receiving necessary treatment for the underlying disease causing low visual acuity. Therefore patients should receive examination by an ophthalmologist before using RETISSA Medical; PMDA instructed the applicant to disseminate this information through the instructions for use. The applicant agreed.

PMDA comprehensively reviewed the conformity of RETISSA Medical to the Essential Principles and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management, the risk management system, and its implementation status in reference to ISO14971:2007 (Medical devices - Application of risk management to medical devices).

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the data on risk management taking into account the discussions in Section "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" and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on in-process control tests for inspection process.

5.B Outline of the review conducted by PMDA

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

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

6.A Summary of the data submitted

The applicant submitted the results of the clinical study conducted in Japan.

6.A.(1) Study design

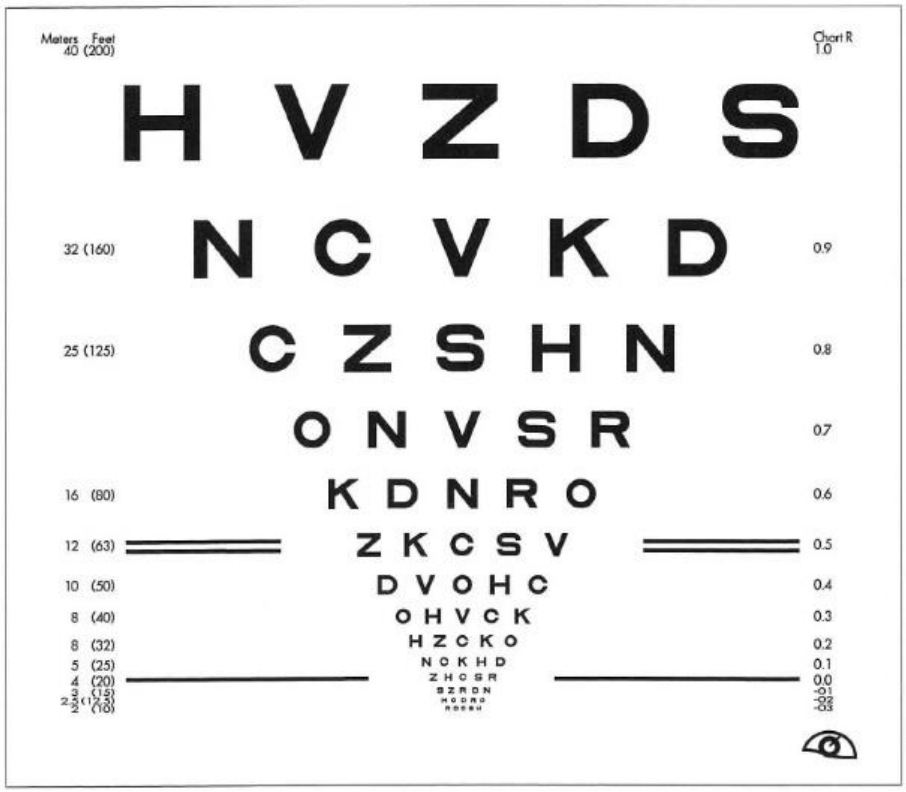
The clinical study was conducted to evaluate the efficacy and safety of RETISSA Medical in patients with low visual acuity caused by anterior eye diseases (mainly irregular astigmatism). The clinical study was conducted in 16 eyes of 15 patients at 2 study sites in Japan from June 23, 2018 (enrollment of the first patient) until October 1, 2018 (last visit of the last patient). The primary endpoint was the change from baseline in the logarithm of the Minimum Angle of Resolution (logMAR) visual acuity in the RETISSA and spectacle groups. The following superiority criterion was defined: RETISSA Medical is considered to be superior to spectacles if "change from baseline in logMAR with RETISSA Medical" minus "change from baseline in logMAR with spectacles" is -0.2 or smaller (i.e., improvement of ≥0.2 versus spectacles). The results of the efficacy endpoint (logMAR measured with

an Early Treatment Diabetic Retinopathy Study [ETDRS] chart) in preceding clinical research of laser eyewear using spectacle-corrected visual acuity as a control, were used to determine a sample size required to show the superiority of RETISSA Medical to spectacles in visual acuity correction. Table 1 shows the outline of the clinical study.

Table 1. Outline of the clinical study

Objective	To evaluate the efficacy and safety of the laser retinal scanning type eyewear in visual acuity correction in patients with low visual acuity caused by anterior eye diseases (mainly irregular astigmatism).
Design	Open-label, single-group, multicenter
Sample size	15 patients (16 eyes)
Number of sites	2 study sites
Inclusion criteria	1. Patients aged ≥18 years at the time of consent 2. Patients with a spectacle-corrected decimal visual acuity of <0.3 measured with the international visual acuity test chart (equivalent to the spectacle-corrected logMAR visual acuity of >0.52 measured with an ETDRS chart [converted value]) (test for each eye) 3. Patients with a target disease (low visual acuity caused by anterior eye diseases [mainly irregular astigmatism]) 4. Patients providing written informed consent to participation in the clinical study
Exclusion criteria	1. Patients with severe dysfunction of the test eye caused by retinal or optic nerve diseases other than the target disease 2. Patients unable to wear the investigational device (e.g., too big or small) 3. Patients with severe nystagmus of the test eye 4. Patients with severe photosensitivity (photophobia) of the test eye 5. Patients planning to undergo surgical intervention of a corneal disease within 3 months after informed consent 6. Patients having undergone surgical intervention of a corneal disease within 6 months before informed consent 7. Patients having undergone surgery of the posterior eye segment in the past 8. Patients planning to use any prohibited concomitant drug during the study period (after enrollment) 9. Patients unable to undergo fundoscopy because of a severe opacity of the anterior eye segment or optic media 10. Patients unable to read alphabets 11. Patients whose first- or second-degree relative(s) is involved in the clinical study as an investigator, subinvestigator, clinical study coordinator, sponsor, etc. 12. Patients being pregnant, nursing, or possibly pregnant 13. Patients having participated in clinical studies of other drugs or medical devices within 30 days before informed consent or participating in those studies during the study period 14. Patients considered to be ineligible for the clinical study by the investigator or subinvestigator
Primary endpoint	Change in logMAR with RETISSA Medical versus spectacles (The change in visual acuity was calculated by subtracting “uncorrected visual acuity” from “RETISSA-corrected visual acuity” or “uncorrected visual acuity” from “spectacle-corrected visual acuity.” The difference in the change between RETISSA Medical and spectacles was determined.)
Secondary endpoints	1. Change tendency in uncorrected visual acuity at each test 2. Change tendency in spectacle-corrected visual acuity at each test 3. Change tendency in RETISSA-corrected visual acuity at each test 4. Comparison of reading speed measured with International Reading Speed Texts (IReST) between RETISSA Medical and spectacles 5. Comparison of maximum reading speed (how fast patients can read) measured with Minnesota READ-Japanese (MNREAD-J) between RETISSA Medical and spectacles 6. Comparison of critical print size (smallest print size at which patients can read with the maximum speed) measured with MNREAD-J between RETISSA Medical and spectacles 7. Comparison of reading acuity (smallest print size at which patients can barely read) measured with MNREAD-J between RETISSA Medical and spectacles 8. Correlation between RETISSA-corrected visual acuity and opacity 9. Correlation between RETISSA-corrected visual acuity and age 10. Change in ETDRS score with 2× digital zoom 11. Malfunctions and adverse events 12. Questionnaire

Observation schedule	Patients visited the study site at Visits 1 and 2 and wore RETISSA Medical. The visual acuity was measured using an ETDRS chart twice at Visit 1 and once at Visit 2.



ETDRS Chart[1)]

Item	Scr	Intervention		FU	Study discontinuation	Post-study follow-up
Visit	0	1		2		
		First	Second			
Day	-28 to -7	0		7-28	Within 7 days after discontinuation[g]	
Written informed consent	○					
Subject characteristics	○					
Inclusion/exclusion criteria	○					
Pregnancy test (urine)	○[a]					
Examination of anterior eye segment	○[b]			○[d]	○	
Intraocular pressure test (air pressure)	○[b]			○[d]	○	
Visual acuity test (international test chart)	○[b]					
Fundoscopy	○[b]			○[d]	○	
Fitting		○		○		
Training			○			
Learning check-up (international test chart)		○[c]	○[c]	○[c]		
Visual acuity test (ETDRS)		○[d]	○[d]	○[d]		
Reading speed (IReST)		○[d]	○[d]			
Reading acuity, etc. (MNREAD-J)[f]			○[d, e]	○[d, e]		
Malfunctions, adverse events		←	→			Δ
Questionnaire			○[d]		○	

○, Essential; Δ, As needed during post-study follow-up; Scr, screening; FU, follow-up.

a Subjects who may possibly be pregnant must undergo urinalysis, except for subjects not of childbearing potential (i.e., postmenopausal for ≥1 year or documented artificial menopause [e.g., hysterectomy, bilateral oophorectomy]).

b Both eyes must be tested except for eyes that cannot be tested or measured (only the test eye is tested at Visit 2 and study discontinuation).

c Performed after fitting or training

d Performed after learning check-up

e Performed with RETISSA Medical at the second test at Visit 1 and with spectacles at Visit 2

f Subjects are evaluated for the maximum reading speed, critical print size, and reading acuity with MNREAD-J.

g Day 0 is defined as the day of discontinuation.

Sample size and analysis population	Enrolled, 15 subjects (16 eyes) Full analysis set (FAS),*3 15 subjects (16 eyes); Per protocol set (PPS),*4 15 subjects (16 eyes)

*1 Training: Patients will wear RETISSA Medical and read a magazine, etc. for ≥30 minutes.
*2 Learning check-up: The visual acuity will be tested using an international visual acuity test chart (Landolt ring).
*3 FAS: All enrolled subjects who have undergone efficacy evaluation at least once. Subjects who do not have the target disease and subjects having no efficacy data at all are excluded from FAS.
*4 PPS: Subjects in FAS who have evaluable data for primary endpoint analysis, excluding subjects who are ineligible, have application violation, concomitant drug/therapy violation (individually assessed based on the drugs/therapies used), or have no evaluable data of the primary endpoint.

6.A.(2) Study results

All subjects enrolled in the clinical study had keratoconus. The uncorrected logMAR visual acuity was 1.490 ± 0.206 (median 1.490 [1.00, 1.70]), while the spectacle-corrected logMAR visual acuity was 1.284 ± 0.224 (median 1.310 [0.86, 1.60]). Table 2 shows the subject characteristics.

Table 2. Subject characteristics

Number of subjects (number of eyes)	N = 15 (N = 16)
Sex	Men 10/16 (62.5%), women 6/16 (37.5%)
Age (years)	43.9 ± 13.1 40.5 [24, 68]
Primary disease	Keratoconus in 16/16 (100%) Stage 4 of Amsler-Krumeich*1 in all subjects
Test eye	Right 4/16 (25.0%), left 12/16 (75.0%)
Uncorrected logMAR*2	1.490 ± 0.206 1.490 [1.00, 1.70] (equivalent to decimal visual acuity 0.032 [converted value]*3)
Spectacle-corrected logMAR*2	1.284 ± 0.224 1.310 [0.86, 1.60] (equivalent to decimal visual acuity 0.048 [converted value]*3)

Continuous variables: Upper, Mean ± standard deviation (SD); Lower, Median [min, max]
Category variables: n/N (%)
*1 Classification based on myopia/astigmatism index, corneal refractive power, scars, and corneal thickness.[2] Stage 4 represents a condition with "a myopia/astigmatism index of unmeasurable refraction," "a corneal refractive power of exceeding 55 diopter," "scars," and "a corneal thickness of ≤200 μm."
*2 The mean and median of the spectacle-corrected visual acuity measured with the international visual acuity test chart at screening were not calculated because it is decimal visual acuity. The visual acuity measured on the day of wearing RETISSA Medical (second test at Visit 1) is presented for reference.
*3 Decimal visual acuity converted from logMAR (logMAR = log [1/decimal visual acuity]).

6.A.(2).(a) Primary endpoint (change in logMAR with RETISSA Medical versus spectacles)

In the clinical study, the first and second visual acuity tests were performed at Visit 1, and the third test at Visit 2 (last visit). Table 3 shows the results. The logMAR was calculated using the formula commonly used in clinical studies using logMAR measured with an ETDRS chart; namely, logMAR = x – 0.02y, where x is the logMAR value of the lowest line in which all of the 5 characters are completely read by the subject and y is the number of letters read in the line just below. Since the endpoint was the change in visual acuity, baseline was defined as uncorrected visual acuity. The change in visual acuity was defined as "RETISSA-corrected visual acuity minus uncorrected visual acuity" or "spectacle-corrected visual acuity minus uncorrected visual acuity."

Table 3. logMAR measured with an ETDRS chart (FAS)

	Uncorrected visual acuity		Spectacle		RETISSA	
	logMAR	Decimal visual acuity (converted value)	logMAR	Decimal visual acuity (converted value)	logMAR	Decimal visual acuity (converted value)
Visit 1 (first test)	1.485 ± 0.235 1.590 [1.06, 1.70]	0.032 0.025	1.360 ± 0.228 1.410 [0.76, 1.64]	0.043 0.038	0.755 ± 0.190 0.700 [0.52, 1.32]	0.175 0.199
Visit 1 (second test)	1.490 ± 0.206 1.490 [1.00, 1.70]	0.032 0.032	1.284 ± 0.224 1.310 [0.86, 1.60]	0.052 0.048	0.889 ± 0.199 0.870 [0.60, 1.24]	0.129 0.134
Visit 2	1.496 ± 0.194 1.560 [1.12, 1.70]	0.031 0.027	1.318 ± 0.250 1.370 [0.72, 1.70]	0.048 0.042	0.831 ± 0.230 0.770 [0.52, 1.32]	0.147 0.169

Continuous variables: Upper, Mean ± SD; Lower, Median [min, max]

logMAR is the common logarithm of visual angle ($\log_{10}$ visual angle). The angle of 2 points the eyes can recognize is called the visual angle (arc-minute). Its reciprocal is decimal visual acuity. Figure 7 shows a correlation between the visual angle and decimal visual acuity. Table 4 shows a correlation between decimal visual acuity and logMAR.

Figure 7. Visual angle and decimal visual acuity

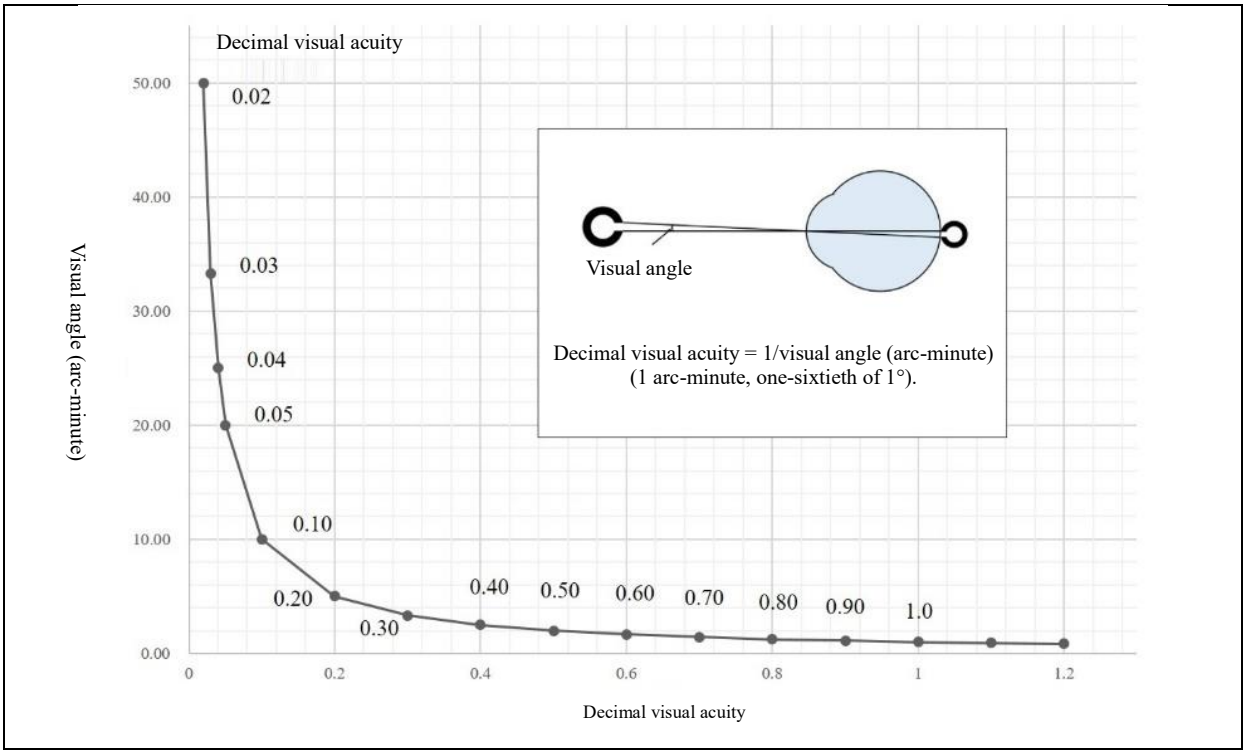


Table 4. Correlation between decimal visual acuity and logMAR

Decimal visual acuity	logMAR	Decimal visual acuity	logMAR	Decimal visual acuity	logMAR	Decimal visual acuity	logMAR
2.0	-0.301	0.8	0.0969	0.09	1.04	0.01	2.00
1.5	-0.176	0.7	0.154	0.08	1.09	0.009	2.04
1.4	-0.146	0.6	0.221	0.07	1.15	0.008	2.09
1.3	-0.113	0.5	0.301	0.06	1.22	0.007	2.15
1.2	-0.0791	0.4	0.397	0.05	1.30	0.006	2.22
1.1	-0.0413	0.3	0.522	0.04	1.39	0.005	2.30
1.0	0.00	0.2	0.698	0.03	1.52	0.004	2.39
0.9	0.0457	0.1	1.00	0.02	1.69	0.003	2.52

Table 5 shows the change in logMAR. The least squares mean of the change in logMAR from baseline value (uncorrected visual acuity) was -0.083 in the spectacle group and -0.688 in the RETISSA group at the first test at Visit 1, and -0.201 in the spectacle group and -0.596 in the RETISSA group at the second test at Visit 1, and -0.164 in the spectacle group and -0.650 in the RETISSA group at Visit 2.

The difference in the least squares mean of the RETISSA group from the spectacle group was -0.605 (linear mixed model, 95% confidence interval [CI] [-0.726, -0.484], $P < 0.001$) at the first test at Visit 1, -0.395 (linear mixed model, 95% CI [-0.549, -0.241], $P < 0.001$) at the second test at Visit 1, and -0.486 (linear mixed model, 95% CI [-0.670, -0.303], $P < 0.001$) at Visit 2.

Table 5. Comparison of change in logMAR (FAS)

N = 16	Visit 1 (first test)		Visit 1 (second test)		Visit 2	
	Spectacle	RETISSA	Spectacle	RETISSA	Spectacle	RETISSA
Least squares mean	-0.083	-0.688	-0.201	-0.596	-0.164	-0.650
95% CI	[-0.225, 0.060]	[-0.830, -0.545]	[-0.338, -0.064]	[-0.733, -0.459]	[-0.308, -0.020]	[-0.794, -0.507]
Difference in least squares mean		-0.605		-0.395		-0.486
95% CI		[-0.726, -0.484]		[-0.549, -0.241]		[-0.670, -0.303]
P-value		<0.001		<0.001		<0.001

6.A.(2).(b) Secondary endpoints

The results of main secondary endpoints are presented below.

i) Comparison of reading speed measured with International Reading Speed Texts (IReST) between RETISSA Medical and spectacles

In the clinical study, reading speed (number of characters per minute [CPM]) was measured at the first and second tests at Visit 1. Table 6 shows the results.

Table 6. Reading speed measured with IReST (FAS)

	Spectacle	RETISSA
Visit 1 (first test)	7.00 ± 28.00 0.00 [0.0, 112.0]	100.31 ± 71.57 111.00 [0.0, 222.0]
Visit 1 (second test)	8.19 ± 32.75 0.00 [0.0, 131.0]	116.00 ± 76.36 109.00 [8.0, 233.0]

Continuous variables: Upper, Mean ± SD; Lower, Median [min, max]

The difference in the least squares mean of the RETISSA group from the spectacle group was 93.3 (linear mixed model, 95% CI [57.1, 129.5], $P < 0.001$) at the first test at Visit 1 and 107.8 (linear mixed model, 95% CI [66.9, 148.8], $P < 0.001$) at the second test at Visit 1.

ii) Comparison of maximum reading speed (how fast subjects can read) measured with Minnesota READ-Japanese (MNREAD-J) between RETISSA Medical and spectacles

In the clinical study, maximum reading speed (CPM) was measured at Visit 1 (second test) and Visit 2. The mean maximum reading speed was 119.6 ± 107.0 (median 91.0 [1.0, 344.0]) in the spectacle group and 163.0 ± 50.7 (median 147.0 [68.0, 248.0]) in the RETISSA group. The difference in the least squares mean of the RETISSA group from the spectacle group was 43.0 (linear mixed model, 95% CI [-16.6, 102.7], $P = 0.145$).

iii) Comparison of critical print size (smallest print size at which subjects can read with the maximum speed) measured with MNREAD-J between RETISSA Medical and spectacles

In the clinical study, critical print size was measured at Visit 1 (second test) and Visit 2. The mean critical print size (point [PT]) was 37.57 ± 13.52 (median 39.40 [8.8, 55.3]) in the spectacle group and 13.73 ± 6.01 (median 14.00 [5.5, 27.8]) in the RETISSA group. The difference in the least squares mean of the RETISSA group from the spectacle group was -23.72 (linear mixed model, 95% CI [-30.78, -16.66], $P < 0.001$).

iv) Comparison of reading acuity (smallest print size at which patients can barely read) measured with MNREAD-J between RETISSA Medical and spectacles

In the clinical study, reading acuity (logMAR) was measured at Visit 1 (second test) and Visit 2. The mean logMAR was 1.063 ± 0.285 (median 1.050 [0.40, 1.40]) in the spectacle group and 0.419 ± 0.168 (median 0.400 [0.10, 0.70]) in the RETISSA group. The difference in the least squares mean of the RETISSA group from the spectacle group was -0.64 (linear mixed model, 95% CI [-0.79, -0.50], $P < 0.001$).

v) Correlation between RETISSA-corrected visual acuity and opacity (effect of opacity on the efficacy of RETISSA Medical)

In the clinical study, slit-lamp microscopy was performed at Visit 0 (screening). The opacity of the cornea and lens was graded using the 4-point scale (none, mild, moderate, and severe) shown in Table 7.

Table 7. Grading of opacity

None	No opacity is observed.
Mild	Opacity is observed, but does not appear to affect the visual function.
Moderate	Opacity appears to affect the visual function.
Severe	Opacity appears to affect the visual function severely.

Table 8 shows the results of the grades of corneal opacity and visual acuity with RETISSA Medical. Corneal opacity was graded as “none” for 1 eye and “mild” for 15 eyes. No patient had moderate or severe opacity. The visual acuity with RETISSA Medical in patients with mild corneal opacity was 0.764 ± 0.193 (median 0.700 [0.52, 1.32]) at the first test at Visit 1, 0.893 ± 0.205 (median 0.920 [0.60, 1.24]) at the second test at Visit 1, and 0.799 ± 0.196 (median 0.720 [0.52, 1.12]) at Visit 2.

Table 8. logMAR by grade of corneal opacity (FAS)

Examination of corneal opacity (Visit 0) Number of test eyes				LEW visual acuity None N = 1	Mild N = 15	Moderate N = 0	Severe N = 0
Measured value	Visit 1	First test	n	1	15	0	0
			Mean	0.620	0.764	-	-
			SD	-	0.193	-	-
			Median	0.620	0.700	-	-
			Min, max	0.62, 0.62	0.52, 1.32	-, -	-, -
			95% CI	[-, -]	[0.657, 0.871]	[-, -]	[-, -]
	Visit 1	Second test	n	1	15	0	0
			Mean	0.820	0.893	-	-
			SD	-	0.205	-	-
			Median	0.820	0.920	-	-
			Min, max	0.82, 0.82	0.60, 1.24	-, -	-, -
			95% CI	[-, -]	[0.780, 1.007]	[-, -]	[-, -]
	Visit 2		n	1	15	0	0
			Mean	1.320	0.799	-	-
			SD	-	0.196	-	-
			Median	1.320	0.720	-	-
			Min, max	1.32, 1.32	0.52, 1.12	-, -	-, -
			95% CI	[-, -]	[0.690, 0.907]	[-, -]	[-, -]

LEW = Laser Eye Wear (RETISSA Medical)

Table 9 shows the results of the grades of lens opacity and visual acuity with RETISSA Medical. Lens opacity was graded as “none” for 14 eyes and “mild” for 1 eye. No patient had moderate or severe opacity. One eye in 1 patient with aphakia was not examined for lens opacity. The visual acuity with RETISSA Medical in 1 patient with mild lens opacity was 0.640 at the first test at Visit 1, 0.820 at the second test at Visit 1, and 0.720 at Visit 2.

Table 9. logMAR by grade of lens opacity (FAS)

Examination of lens opacity (Visit 0) Number of test eyes				LEW visual acuity None N = 14	Mild N = 1	Moderate N = 0	Severe N = 0
Measured value	Visit 1	First test	n	14	1	0	0
			Mean	0.761	0.640	-	-
			SD	0.201	-	-	-
			Median	0.700	0.640	-	-
			Min, max	0.52, 1.32	0.64, 0.64	-, -	-, -
			95% CI	[0.645, 0.877]	[-, -]	[-, -]	[-, -]
	Visit 1	Second test	n	14	1	0	0
			Mean	0.891	0.820	-	-
			SD	0.213	-	-	-
			Median	0.870	0.820	-	-
			Min, max	0.60, 1.24	0.82, 0.82	-, -	-, -
			95% CI	[0.769, 1.014]	[-, -]	[-, -]	[-, -]
	Visit 2		n	14	1	0	0
			Mean	0.850	0.720	-	-
			SD	0.241	-	-	-
			Median	0.840	0.720	-	-
			Min, max	0.52, 1.32	0.72, 0.72	-, -	-, -
			95% CI	[0.711, 0.989]	[-, -]	[-, -]	[-, -]

LEW = Laser Eye Wear (RETISSA Medical)

6.A.(2).(c) Malfunctions

No malfunction was reported in the clinical study.

6.A.(2).(d) Adverse events

Adverse events reported in the clinical study were mild conjunctival hyperaemia (1 event, 6.3%) and mild nasopharyngitis (1 event, 6.3%). Conjunctival hyperaemia was caused by the subject's sleep shortage; its causal relationship to RETISSA Medical was ruled out by the investigator. The causal relationship between nasopharyngitis and RETISSA Medical was ruled out by the investigator because the site of the adverse event (nasopharyngitis) was unrelated to the test eye.

6.B Outline of the review conducted by PMDA

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

(1) Appropriateness of evaluating the efficacy of RETISSA Medical based on the results of the clinical study
(2) Appropriateness of safety evaluation of RETISSA Medical
(3) Clinical positioning of RETISSA Medical
(4) Post-marketing safety measures

6.B.(1) Appropriateness of evaluating the efficacy of RETISSA Medical based on the results of the clinical study

6.B.(1).(a) Results of the primary endpoint

The applicant's explanation:

A clinical study registered in the University Hospital Medical Information Network (UMIN) used logMAR measured with an ETDRS chart as an efficacy endpoint. Another clinical study that investigated improvement in visual acuity used an increase of 10 characters (corresponding to logMAR of 0.2) as an efficacy endpoint. Based on these studies, the following primary endpoint (superiority criterion) was defined: RETISSA Medical is considered to be superior to spectacles if "change from baseline in logMAR with RETISSA Medical" minus "change from baseline in logMAR with spectacles" is -0.2 or smaller (i.e., improvement of ≥0.2 versus spectacles). According to the preceding clinical research using the prototype of RETISSA Medical having the same specifications for projection to the retina, the difference in the least squares mean of logMAR of the prototype from spectacles was -0.69. To obtain a difference in least squares mean of -0.2 in the clinical study, 13 eyes were required with the power of 80%. Allowing for a dropout rate of approximately 10%, the target sample size of 15 eyes was determined. In the clinical study, the difference between the RETISSA group and the spectacle group was -0.395 (linear mixed model, 95% CI [-0.549, -0.241], $P < 0.001$), demonstrating the efficacy of RETISSA Medical.

PMDA's view:

1) Study design

Since RETISSA Medical is intended to correct visual acuity, it is appropriate to use logMAR measured with an ETDRS chart as the primary endpoint. As described later in Section "6.B.(3) Clinical positioning of RETISSA Medical," patients with a severe corneal deformation may feel discomfort or

pain because of mechanical friction when they wear a hard contact lens. In addition, hard contact lenses may fall off when their shapes do not match the corneal shapes of patients. To improve their daily lives, those patients wear eyeglasses or soft contact lenses, which do not fully correct visual acuity, and use an optical aid (e.g., magnifying glass and magnifier reading aid) as needed. There is no consensus about how much change in visual acuity should be regarded as "improvement" in anterior eye diseases. However, research that measured visual acuity with an ETDRS chart at various distances in patients with refraction errors reported that sensitivity and specificity were maintained when a change in logMAR visual acuity was ≥0.2.[7)] Other research reported that even patients with stable eye diseases showed a 0.16 change in logMAR visual acuity.[8)] Taking account of the results of the Expert Discussion, it is appropriate to define "improvement in visual acuity" as an increase of 10 characters (corresponding to logMAR of 0.2) with RETISSA Medical compared with spectacles.

Spectacles were used as the control in the clinical study. Since patients who have difficulty in wearing a hard contact lens may wear eyeglasses or soft contact lenses, which do not fully correct visual acuity, it is appropriate to show an improvement in logMAR with RETISSA Medical in comparison with spectacles.

The sample size was determined based on the results of the efficacy endpoint (logMAR measured with an ETDRS chart) in the preceding clinical research conducted in 15 eyes of 11 patients with keratoconus to evaluate the prototype of RETISSA Medical having the same specifications for projection to the retina. The clinical research showed a logMAR of 0.84 ± 0.51 (equivalent to a decimal visual acuity of 0.144 [converted value]) with spectacles and 0.50 ± 0.13 (equivalent to a decimal visual acuity of 0.316 [converted value]) with the prototype. Based on these results, the sample size of the clinical study was calculated and determined to show the superiority of RETISSA Medical to spectacles in visual acuity correction. Thus, the samples size is appropriate.

Reference data: Summary of the preceding clinical research

<table>
<tr><td>Objective</td><td colspan="3">To measure visual acuity with the laser retinal scanning type eyewear in patients with keratoconus</td></tr>
<tr><td>Design</td><td colspan="3">Open-label, single-group, single-center</td></tr>
<tr><td>Sample size</td><td colspan="3">11 patients (15 eyes)</td></tr>
<tr><td>Endpoint</td><td colspan="3">logMAR (controls: spectacle group and hard contact lens group)</td></tr>
<tr><td>Results</td><td colspan="3"><table>
<tr><td></td><td>logMAR</td><td>Decimal visual acuity (converted value)</td></tr>
<tr><td>Uncorrected visual acuity</td><td>1.28 ± 0.41</td><td>0.052</td></tr>
<tr><td>Spectacle</td><td>0.84 ± 0.51</td><td>0.144</td></tr>
<tr><td>Hard contact lens</td><td>0.10 ± 0.27</td><td>0.794</td></tr>
<tr><td>Prototype</td><td>0.50 ± 0.13</td><td>0.316</td></tr>
</table></td></tr>
</table>

As explained about the safety in Section "2.(4) Radiation safety," it is appropriate to observe patients whey they wear RETISSA Medical twice at Visit 1 and once at Visit 2 (and during the post-discontinuation follow-up period in patients who discontinue the clinical study). The normal view system focuses an incident light on the retina using the refractive power of the cornea or lens. RETISSA Medical uses a Maxwellian view system that delivers a visible RGB laser beam to the retina and thereby focuses images on the retina without depending on the refractive power of the cornea or lens. Since both systems use a similar principle that a light beam is focused on the retina, it is

appropriate to evaluate the efficacy when patients wear RETISSA Medical twice at Visit 1 and once at Visit 2.

The clinical study was conducted in an open-label, single-group design where each patient received all interventions. This study design is appropriate because RETISSA Medical does not depend on the refractive power of the cornea or lens to correct visual acuity while spectacle correction affects the subject's ability of controlling the refractive power.

2) Study results

In the clinical study, visual acuity was measured 3 times. In each visual acuity test, "change from baseline in logMAR with RETISSA Medical" minus "change from baseline in logMAR with spectacles" was smaller than -0.2. RETISSA Medical improved logMAR compared with spectacles, which are a conventional visual acuity correction method; the difference was statistically significant. At the second test at Visit 1, the difference in logMAR in the RETISSA group from the spectacle group was -0.395 (linear mixed model, 95% CI [-0.549, -0.241], $P < 0.001$), which was the smallest difference among the 3 tests. In summary, the change in logMAR showed a statistically significant difference of -0.395 between the RETISSA and spectacle groups. This difference exceeded 10 characters (corresponding to the logMAR of 0.2). Taking account of the results of the Expert Discussion, PMDA concluded that the clinical efficacy of RETISSA Medical can be evaluated on the basis of the above results in patients who have difficulty in wearing a hard contact lens and fail to achieve enough visual acuity with eyeglasses or soft contact lenses.

6.B.(1).(b) Disease for which RETISSA Medical is indicated

PMDA asked the applicant to explain why the target disease of the clinical study was keratoconus when the proposed intended use was "anterior eye diseases (mainly irregular astigmatism)."

The applicant's response:

Keratoconus, the disease evaluated in the clinical study, is characterized by corneal herniation or deformation due to thinning of the corneal center. A laser beam is locally delivered to the center of the pupil of a patient with an irregular corneal deformation and scans and dots the retina, thereby directly projecting images on the retina. RETISSA Medical is, therefore, effective on reduced visual acuity caused by a shape abnormality of the anterior eye segment, namely, irregular astigmatism.

PMDA's view on the applicant's response:

Irregular astigmatism, which cannot be fully corrected by a cylindrical lens, is a refraction error caused by the irregular refracting surface. Irregular astigmatism is caused by keratoconus, pellucid marginal corneal degeneration, pterygium etc. RETISSA Medical uses a Maxwellian view system based on the nature of the laser beam that travels in a straight line. Therefore RETISSA Medical is expected to be effective without depending on the refractive power of the cornea or lens. Pellucid marginal corneal degeneration is characterized by thinning or deformation of the corneal center, and a pterygium is a growth of the conjunctiva over the cornea. Both diseases create an irregular refracting surface. PMDA concluded that the efficacy of RETISSA Medical in patients with irregular astigmatism with an irregular refracting surface can be evaluated on the basis of efficacy data from

patients with keratoconus, who have an irregular refracting surface due to corneal thinning or deformation.

The anterior eye segment includes the eyelids, conjunctiva, and cornea. Anterior eye diseases therefore include diseases unrelated to refraction errors, such as conjunctivitis and keratitis. The clinical study was conducted in patients with keratoconus. Taking account of comments raised in the Expert Discussion, the proposed intended use "anterior eye diseases (mainly irregular astigmatism)" should be changed to "irregular astigmatism."

6.B.(1).(c) Effect of opacity on the efficacy of RETISSA Medical

RETISSA Medical is intended to be used in patients with irregular astigmatism. Patients who have opacity of cornea and lens, which are optical media, are also expected to use RETISSA Medical in clinical practice. PMDA asked the applicant to explain the correlation between the severity of opacity and efficacy.

The applicant's response:

In the clinical study, no patient had moderate or severe opacity. Although the correlation between moderate or severe opacity and visual acuity with RETISSA Medical has not been evaluated, RETISSA Medical provided satisfactory correction of visual acuity in patients with mild opacity.

PMDA's view on the applicant's response:

Corneal or lens opacity is classified based on its site and description.[9), 10)] In the clinical study, opacity was classified based on the level of its effect on visual function or severity. As shown in Table 8, corneal opacity was graded as "None" for 1 eye and "Mild" for 15 eyes. As shown in Table 9, lens opacity was graded as "None" for 14 eyes and "Mild" for 1 eye. No patient had moderate or severe opacity. Thus, in the clinical study, the effect of moderate or severe opacity on the efficacy of RETISSA Medical was not evaluated.

Given the principle of RETISSA Medical, if the opacity of the optic media is severe enough to interrupt the path of a laser beam (visible light), the laser beam is scattered and does not reach the retina, failing to correct visual acuity. Opacity is classified based on its site and description, but patients in clinical practice have various levels and forms of opacity. Since the presence of opacity in the pathway of a laser beam may affect the efficacy of RETISSA Medical, it is difficult to investigate the correlation between the opacity and efficacy of RETISSA Medical comprehensively in all situations that are expected to be encountered in clinical practice.

Taking account of comments raised in the Expert Discussion, PMDA concluded that the following information should be disseminated through the instructions for use:

(a) RETISSA Medical was shown to correct visual acuity of patients who were classified as having mild opacity according to the grading criteria used in the clinical study. (b) The opacity of the optic media scatters a laser beam, which may result in reduced efficacy.

6.B.(1).(d) Reading speed

The applicant's explanation:

Comparisons of (a) reading speed measured with IReST, (b) critical print size measured with MNREAD-J, and (c) reading acuity measured with MNREAD-J, showed significant differences between RETISSA Medical and spectacles in all tests. These endpoints were determined based on everyday use condition. The RETISSA Medical was shown to be superior to the spectacles, indicating the clinical significance of replacing spectacles by RETISSA Medical. A comparison of maximum reading speed measured with MNREAD-J showed no significant difference between RETISSA Medical and spectacles in any test.

PMDA's view:

The secondary endpoints that evaluated improvement in reading, etc. by visual acuity correction also showed an improving tendency, supporting the results of the primary endpoint. Research on reading speed in subjects including 36 Japanese subjects aged 18 to 35 years without any visual function abnormality reported a reading speed of 357 ± 56 characters as measured with IReST.[11)] Research in 9 Japanese subjects at the mean age of 21.1 ± 3.7 years having a decimal visual acuity of ≥1.0 without any visual function abnormality reported a reading speed of approximately 300 characters as measured with MNREAD-J chart with critical print size.[12)] The results of these evaluation methods involving reading of characters and texts may depend on the age or educational level of subjects. However, in the clinical study, for example, reading speed (CPM) measured with IReST at Visit 1 (second test) showed greater improvement with RETISSA Medical (116.00 ± 76.36 [median 109.00 (8.0, 233.0)]) than with spectacles (8.19 ± 32.75 [median 0.00 (0.0, 131.0)]). This indicates no particular problem with this efficacy evaluation method or results.

6.B.(2) Appropriateness of safety evaluation of RETISSA Medical

Adverse events reported in the clinical study were mild conjunctival hyperaemia (1 event, 6.3%) and mild nasopharyngitis (1 event, 6.3%). Their causal relationship to RETISSA Medical was ruled out by the investigator. Both adverse events are considered unrelated to RETISSA Medical. PMDA asked the applicant to explain the incidence of adverse events with preceding consumer products using the same laser output as RETISSA Medical.

The applicant's response:

No serious adverse event (e.g., retinal disorder) has been reported with preceding consumer products. Previous clinical experience shows that patients with myodesopsia may experience aggravation of the symptom while the laser beam is passing through the eye and may have asthenopia after use. This information will be provided in the adverse event section of the instructions for use.

PMDA's view:

In the clinical study, patients used RETISSA Medical only for a limited duration of time. Although patients may use RETISSA Medical for a longer period of time according to their life style in clinical practice, the applicant's explanation that the safety of RETISSA Medical is assured is reasonable for the reason described above and based on the results of nonclinical study described in Section "2.(4) Radiation safety."

Fundoscopy and OCT performed in patients with keratoconus in the clinical study showed no retinal disorder. Since the clinical study enrolled patients with keratoconus, but no patients with retinal disease, the effect of laser irradiation in patients with retinal disease was not investigated. RETISSA Medical is a medical device that delivers a laser beam to the retina, and is indicated for irregular astigmatism. However, patients with retinal disease might consider the use of RETISSA Medical in clinical practice. Taking account of comments raised in the Expert Discussion, PMDA concluded that the following information should be disseminated through the instructions for use:

The safety of RETISSA Medical has not been established in patients with retinal disease because this patient population has not been exposed to laser radiation from RETISSA Medical.

6.B.(3) Clinical positioning of RETISSA Medical

The applicant's explanation:

RETISSA Medical offers a new option, including a temporal alternative correction, for patients who fail to achieve enough visual acuity correction by the conventional correction methods or cannot continuously use those methods because of discomfort or pain.

PMDA's view on the applicant's response:

RETISSA Medical corrects the visual acuity of only 1 eye but not both eyes and cannot be worn all the time unlike eyeglasses or contact lenses. With the AC adapter, RETISSA Medical can be used continuously. With the built-in battery charged for approximately 6 hours, it can operate for approximately 100 minutes. Since RETISSA Medical uses a Maxwellian view system and a laser beam passing through the center of the pupil, if the laser beam misses the pupil and hits the iris, sclera, etc., images are not focused on the retina, failing to correct visual acuity. Because the pupil size is approximately 4 mm in bright light,[13)] RETISSA Medical limits user's movements compared with eyeglasses or contact lenses. Patients are, therefore, not expected to wear RETISSA Medical all the time. RETISSA Medical should be positioned as a device that assists patients in reading, etc.

As described in Section "6.B.(1).(b) Disease for which RETISSA Medical is indicated," patients with irregular astigmatism, the target disease of RETISSA Medical, have an irregular refracting surface and have difficulty in wearing a hard contact lens because of discomfort or pain due to mechanical friction caused by a hard contact lens. These patients also fail to achieve enough visual acuity with eyeglasses or soft contact lenses. The inclusion criterion in the clinical study was "Patients with a spectacle-corrected decimal visual acuity of <0.3" and, as presented in Table 2 in Section "6.A.(2) Study results," patients enrolled in the clinical study had a spectacle-corrected logMAR visual acuity of 1.284 ± 0.224 (median 1.310 [0.86, 1.60]) (corresponding to a decimal visual acuity of 0.048 [converted value]). Thus, RETISSA Medical should be indicated for patients who cannot achieve enough visual acuity by conventional correction methods. RETISSA Medical benefits patients with eyes having an irregular refracting surface because it corrects visual acuity without a hard contact lens that comes in contact with the refracting surface. Taking account of comments raised in the Expert Discussion, PMDA concluded that RETISSA Medical has a clinical significance because it offers an option for visual acuity correction in irregular astigmatism.

Taking account of comments raised in the Expert Discussion, however, PMDA concluded that the wording "patients with vision disorders" in the proposed intended use should be changed to "patients whose vision is affected by irregular astigmatism (whose vision cannot be corrected sufficiently by conventional glasses or contact lenses)" because the endpoints of the clinical study were visual acuity.

6.B.(4) Post-marketing safety measures

6.B.(4).(a) Information to be provided to ensure proper use (contents of the instructions for use)

The presence of opacity in the optic media, the path of a laser beam, compromises the efficacy of RETISSA Medical because it scatters the laser beam. The condition of the optic media needs to be evaluated prior to the use of RETISSA Medical. RETISSA Medical is a medical device that delivers a laser beam to the retina. The function of the patient's retina, which serves as a screen, directly affects the efficacy of RETISSA Medical. As explained in Section "6.B.(2) Appropriateness of safety evaluation of RETISSA Medical," the effect of laser irradiation in patients with retinal disease has not been evaluated. The retinal function should be examined prior to the use of RETISSA Medical to prevent unnecessary laser irradiation in patients with retinal disease, who are not expected to respond to this therapy.

If a patient with low visual acuity of unidentified cause uses RETISSA Medical without undergoing an examination by an ophthalmologist, they may suffer a delay in receiving necessary treatment for the underlying disease causing low visual acuity. Patients should undergo examination by an ophthalmologist before using RETISSA Medical.

Taking account of comments raised in the Expert Discussion, PMDA concluded that the following information should be disseminated through the instructions for use:

> Patients should receive examination of the optic media and retina by an ophthalmologist before using RETISSA Medical.

6.B.(4).(b) Necessity of use results evaluation

The safety of the laser beam is assured as discussed in Section "2.(4) Radiation safety." In addition, as described in Section "6.B.(2) Appropriateness of safety evaluation of RETISSA Medical," no clinically significant adverse event was identified in the clinical study. Thus the necessary safety evaluation of RETISSA Medical has already been performed in the pre-marketing setting.

As for efficacy, the normal view system focuses images on the retina using the refractive power of the cornea and lens, while RETISSA Medical uses a Maxwellian view system that delivers a visible RGB laser beam to the retina and thereby focuses images on the retina without depending on the refractive power of the cornea or lens. In the clinical study, a comparison of the change from baseline in logMAR between the RETISSA group and the spectacle group showed a statistically significant difference of -0.395 in favor of the RETISSA group. This difference exceeded 10 characters (corresponding to the logMAR of 0.2), indicating that the visible RGB laser beam from RETISSA Medical can correct visual acuity. RETISSA Medical uses a laser retinal scanning technology, which has already been used in ophthalmic medical devices, including OCT, which is a diagnostic imaging

modality that examines the posterior segment of the eye (term name: Ophthalmic camera, controlled medical device [Class II]) and laser ophthalmoscopes (term name: Ophthalmic camera, controlled medical device [Class II]) in clinical practice. Taking account of comments raised in the Expert Discussion, PMDA concluded that the necessity of use results evaluation is low and therefore RETISSA Medical need not be designated as a medical device subject to a use results evaluation.

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

As described in Section 6, PMDA concluded that RETISSA Medical need not be subject to a use results evaluation.

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

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

The new medical device application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of 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.

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

The new medical device application data were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

RETISSA Medical is a laser projector eyewear that delivers a laser beam to the retina to correct visual acuity in patients with low visual acuity caused by irregular astigmatism. The PMDA's reviews of RETISSA Medical were focused on (1) appropriateness of evaluating the efficacy of RETISSA Medical based on the results of the clinical study, (2) appropriateness of safety evaluation of RETISSA Medical, (3) clinical positioning of RETISSA Medical, and (4) post-marketing safety measures. Based on comments raised in the Expert Discussion, PMDA reached the following conclusions.

(1) Appropriateness of evaluating the efficacy of RETISSA Medical based on the results of the clinical study

The applicant submitted the results of a Japanese clinical study as clinical data of RETISSA Medical. The change in logMAR showed a statistically significant difference of -0.395 between the RETISSA and spectacle groups in favor of the RETISSA group. This difference exceeded 10 characters (corresponding to the logMAR of 0.2). Therefore the clinical efficacy of RETISSA Medical can be

evaluated on the basis of the above results in patients who have difficulty in wearing a hard contact lens and fail to achieve enough visual acuity with eyeglasses or soft contact lenses.

RETISSA Medical uses a Maxwellian view system based on the nature of the laser beam that travels in a straight line, and is expected to be effective in the target disease without depending on the refractive power of the cornea or lens. PMDA concluded that the efficacy of RETISSA Medical in patients with irregular astigmatism with an irregular refracting surface can be evaluated on the basis of efficacy data from patients with keratoconus, who have an irregular refracting surface due to corneal thinning or deformation.

The proposed intended use is anterior eye diseases (mainly irregular astigmatism); this term includes not only irregular astigmatism but also other diseases of the anterior segment of the eye (i.e., the eyelid, conjunctiva, and cornea). Taking account of comments raised in the Expert Discussion, PMDA concluded that the proposed intended use "Anterior eye diseases (mainly irregular astigmatism)" should be changed to "Irregular astigmatism."

The effect of opacity on the efficacy of RETISSA Medical could not be evaluated based on the results of the clinical study. In view of the principle of RETISSA Medical, the presence of opacity in the pathway of a laser beam may affect its efficacy. It is difficult to investigate the correlation between the opacity and efficacy of RETISSA Medical comprehensively to cover all situations that are expected to be encountered in clinical practice. Taking account of comments raised in the Expert Discussion, PMDA concluded that the following information should be disseminated through the instructions for use:

> (a) The clinical study demonstrated that RETISSA Medical can correct visual acuity in patients with mild opacity. (b) The opacity of the optic media may scatter a laser beam and thereby reduce the efficacy.

(2) Appropriateness of safety evaluation of RETISSA Medical

Adverse events reported in the clinical study were mild conjunctival hyperaemia (1 event, 6.3%) and mild nasopharyngitis (1 event, 6.3%).

Fundoscopy and OCT performed in patients with keratoconus in the clinical study showed no retinal disorder. Since the clinical study enrolled no patients with retinal disorder, the effect of laser irradiation in patients with retinal disease was not investigated. Taking account of comments raised in the Expert Discussion, PMDA concluded that the following information should be disseminated through the instructions for use:

> The safety of RETISSA Medical has not been established in patients with retinal disease because this patient population has not been exposed to laser radiation from RETISSA Medical.

(3) Clinical positioning of RETISSA Medical

RETISSA Medical corrects the visual acuity of only 1 eye but not both eyes and cannot be worn all the time unlike eyeglasses or contact lenses. With the AC adapter, RETISSA Medical can be used continuously. With the built-in battery charged for approximately 6 hours, it can operate for

approximately 100 minutes. Since RETISSA Medical uses a Maxwellian view system and a laser beam passing through the center of the pupil, if the laser beam misses the pupil and hits the iris, sclera, etc., images are not focused on the retina, failing to correct visual acuity. RETISSA Medical limits user's movements compared with eyeglasses or contact lenses, which prevents patients from wearing RETISSA Medical all the time. RETISSA Medical should be positioned as a device that assists patients in reading, etc.

Patients with irregular astigmatism, the target disease of RETISSA Medical, have an irregular refracting surface and have difficulty in wearing a hard contact lens because of discomfort or pain due to mechanical friction caused by a hard contact lens. These patients fail to achieve enough visual acuity with eyeglasses or soft contact lenses. RETISSA Medical benefits patients with eyes having an irregular refracting surface because it corrects visual acuity without a hard contact lens that comes in contact with the refracting surface. Taking account of comments raised in the Expert Discussion, PMDA concluded that RETISSA Medical has a clinical significance because it offers an option for visual acuity correction in irregular astigmatism.

Taking account of comments raised in the Expert Discussion, however, PMDA concluded that the wording "patients with vision disorders" in the proposed intended use should be changed to "patients whose vision is affected by irregular astigmatism (whose vision cannot be corrected sufficiently by conventional glasses or contact lenses)" because the endpoints of the clinical study were visual acuity.

(4) Post-marketing safety measures

In the review on the information to be provided to promote proper use (contents of the instructions for use), PMDA concluded that the condition of the optic media should be evaluated prior to the use of RETISSA Medical because the presence of opacity in the optic media, the path of a laser beam, scatters the laser beam and thereby compromises the efficacy of RETISSA Medical. RETISSA Medical is a medical device that delivers a laser beam to the retina. The function of the patient's retina, which serves as a screen, directly affects the efficacy of RETISSA Medical. Since the effect of laser irradiation in patients with retinal disease has not been evaluated, the retinal function should be examined prior to the use of RETISSA Medical to prevent unnecessary laser irradiation in patients with retinal disease, who are not expected to respond to this therapy.

If a patient with low visual acuity of unidentified cause uses RETISSA Medical without undergoing an examination by an ophthalmologist, they may suffer a delay in receiving necessary treatment for the underlying disease causing low visual acuity. Patients should undergo examination by an ophthalmologist before using RETISSA Medical. Taking account of comments raised in the Expert Discussion, PMDA concluded that the following information should be disseminated through the instructions for use:

> Patients should receive examination of the optic media and retina by an ophthalmologist before using RETISSA Medical.

PMDA also discussed the necessity of use results evaluation. The safety of the laser beam is assured as discussed in Section "2.(4) Radiation safety." In addition, no clinically significant adverse event was

identified in the clinical study. PMDA concluded that the necessary safety evaluation of RETISSA Medical has already been performed in the pre-marketing setting.

As for the efficacy, the clinical study showed a statistically significant difference (-0.395) in the change from baseline in logMAR in favor of the RETISSA group compared with the spectacle group. This difference exceeded 10 characters (corresponding to the logMAR of 0.2), indicating that the visible RGB laser beam from RETISSA Medical can correct visual acuity. RETISSA Medical uses a laser retinal scanning technology, which has already been used in ophthalmic medical devices, including OCT, which is a diagnostic imaging modality that examines the posterior segment of the eye and laser ophthalmoscopes in clinical practice. Taking account of comments raised in the Expert Discussion, PMDA concluded that the necessity of use results evaluation is low and therefore RETISSA Medical need not be designated as a medical device subject to a use results evaluation.

On the basis of the above discussions, PMDA concludes that the product may be approved for the following intended use.

Intended Use
RETISSA Medical is intended to correct the visual acuity of patients whose vision is affected by irregular astigmatism (whose vision cannot be corrected sufficiently by conventional glasses or contact lenses).

The product is not classified as a biological product or a specified biological product.

PMDA has concluded that the present application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

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