Clinical evaluation of DAILIES TOTAL 1® Multifocal compared to 1-Day Acuvue® Moist® Multifocal in a Japanese population.

CLINICAL STUDY PROTOCOL

Alcon Japan Ltd.

1-23-1 Toranomon, Minato-ku, Tokyo

Protocol No.: CLJ369-P001 / NCT03341923
Project No.: A03218
Version 1.1: 22 JAN, 2018

SUMMARY

Protocol No.	CLJ369-P001
Objective	The purpose of this clinical study is to demonstrate non-inferiority of DAILIES TOTAL1® (DT1MF) Multifocal contact lenses to 1-DAY ACUVUE® Moist® Multifocal (AMMF) for Investigator-graded successful lens centration in Japanese population.
Subjects	Habitual presbyopic soft/ silicone hydrogel contact lens wearers (multifocal (MF) lenses only) with a near spectacle ADD of +0.50D to +2.50D (inclusive).
Study Design	Prospective, Multi-Center, Single Masked (Subject), Randomized, Crossover study.
Investigational Products	DAILIES TOTAL1® Multifocal (DT1MF) 1-DAY ACUVUE® Moist® (Multifocal) (AMMF)
Variables	[Efficacy] Primary Efficacy: Investigator-graded successful lens centration of “Optimal” after 14±3 days of wearing. [redacted]

	 [Safety] • Biomicroscopy findings: Slit-lamp examination • Best corrected visual acuity with trial frame • Adverse events • Device deficiencies
Usage	Follow the direction for use.
Examinations Schedule	• Visit 1: Study start day (Baseline visit) • Visit 2: Follow up visit after 14±3 days of Visit 1 • Visit 3: Follow up visit after 14±3 days of Visit 2
No. of Subjects	Required: 120 subjects (at least 50% should be wearing Proclear 1 day MF contact lenses habitually, 1 eye per 1 subject is the analysis target) Planned: 134 subjects
Study period	From NOVEMBER 2017 to OCTOBER 2018
Study Sponsor	Alcon Japan Ltd.
GCP	This study will be conducted in accordance with Good Clinical Practice (GCP) and the Ethical Guidelines for Clinical Studies (2014, Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare Notification No.3, partial revision on 28 February, 2017), in principle.

Amendment

Purpose of amendment:

The purpose of this amendment is to make a clarification of typo this protocol.

Current study status:

Case Report Form Revision Required:	☐	Yes	☒	No		
Informed Consent Modifications Required:	☐	Yes	☒	No		
Applicable Investigators:	☐	All	☐	Selected (list below)	☒	No

Itemized Changes:

Items	Protocol ver.1.0	Protocol ver. 1.1
6. STUDY PROCEDURE (2) Examinations Schedule Table Examinations Schedule	Adverse events	Adverse events, Device Deficiencies
	*1: Allowance for next visit: the day after 11 to 14 days from the present visit.	*1: Allowance for next visit: the day after 14 ± 3 days from the present visit.

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1. INTRODUCTION

(1) Circumstances

Presbyopia is defined as the normal loss of accommodation that occurs with age[1], where the cause of the loss is associated with the sclerosis of crystalline lens[1]. It has been reported that the sclerosis of crystalline lens exponentially increases at around age 45[1]. While there are many ways to correct presbyopia such as eye glasses, contact lenses (CL) and keratomileusis (a corneal reshaping surgery to correct presbyopia or multifocal intra ocular lens)[2], the use of multifocal type CL (MFCL) to correct presbyopia is gradually increasing[3]. However, it has been reported that there are more people who are discontinuing the use of CL due to discomfort and visual acuity issues above age 40 for whom it is considered necessary to correct presbyopia than the people below age 40[4].

Alcon Japan Ltd., has launched DAILIES TOTAL1® Multifocal (DT1MF), the silicone hydrogel contact lenses that are superior in comfort[5] in July, 2017. DT1MF adopts the optical design with progressive add power by adding add power to realize seamless visual performance concentrically[6]. It is considered that center stability of MFCL on cornea when wearing CL is critical in terms of visual performance of contact lenses[7], lens centration, lens fitting, subjective ratings (overall quality of vision, lens comfort at the end of a day, visual performance (far, intermediate(distance) and near), eye fatigue (stiff shoulder, headache, dry eye, eye pain, heavy feeling in the back of eyes, eyestrain), lens comfort throughout the day), binocular VA (far, intermediate, near), corneal staining, conjunctival staining, lens surface wettability and lens deposit will be assessed in comparison to 1-Day ACUVUE® MOIST® Multifocal (AMMF)[8] contact lenses similar to DT1MF in the optical design which uses hydroxyethyl methacrylate in the material as a control.

This study will be conducted in accordance with Good Clinical Practice (GCP) and the Ethical Guidelines for Clinical Studies (2014, Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare Notification No.3, partial revision on 28 February, 2017), in principle.

(2) Summary of known and possible risks and benefits to subjects

Regarding the investigational devices assessed in this study, DT1MF and AMMF, Alcon Japan Ltd., and Johnson & Johnson K.K. Vision Care Company, respectively, were granted marketing approval in Japan in February 2017 and December 2014, respectively. The safety and efficacy information on the two investigational devices are described below.

1) Information on Safety

[1] Items common to DT1MF and AMMF

The following warnings and contraindications stated in direction for use are common to both investigational devices:

[Warnings]

- Contact lens wear could result in corneal epithelial problems including corneal ulcer, keratitis (including infectious keratitis), corneal infiltration, and corneal erosion, as well as corneal edema, conjunctivitis (including giant papillary conjunctivitis), iritis, and corneal neovascularization, and may accelerate a decrease in corneal endothelial cells.

[Contraindications]

- Acute and subacute inflammations of anterior eye segment
- Eye infection
- Uveitis
- Decreased corneal sensitivity
- Dry eye and lacrimal disease that may interfere with lens wear
- Eyelid abnormality
- Allergic disease that may affect lens wear
- Living environments constantly exposed to dryness
- Living environments liable to eye contamination with dust or drugs
- Other diseases inappropriate for lens wear

[2] Information on Safety for DT1MF

Information on device deficiency and adverse events stated in direction for use of DT1MF is described below:

Deficiency/Adverse events

The following deficiency and adverse events may occur:

(1) Device Deficiency

Lens: Tear, scratch, deformation, discoloration

(2) Adverse events

Corneal ulcer, corneal abscess, corneal perforation, corneal infiltration, corneal erosion, keratitis, Corneal epithelial disorders including corneal epithelial staining, corneal edema, corneal neovascularization, conjunctivitis(including allergic conjunctivitis and giant papillary conjunctivitis), subconjunctival hemorrhage, iritis, hordeolum, meibomitis, chalazion, accommodative asthenopia, dry eye, and decreased corneal endothelial cells, photosensitivity reaction(photophobia), rainbows and aureole around light

[3] Information on Safety for AMMF

Information on device deficiency and adverse events stated in direction for use of AMMF is described below:

Deficiency/Adverse events

The following deficiency and adverse events may occur:

(1) Device Deficiency

Lens: Tear, scratch, deformation, discoloration, foreign object, 2 lenses of more attached to each other in a layer

Preservative solution and package: Leakage, discoloration/deterioration of liquid, breakage, contamination

(2) Adverse events

Corneal ulcer, corneal abscess, corneal perforation, corneal infiltration, corneal erosion, keratitis, Corneal epithelial disorders including corneal epithelial staining, corneal edema, corneal neovascularization, conjunctivitis, subconjunctival hemorrhage, iritis, hordeolum, meibomitis, chalazion, accommodative asthenopia, dry eye, and decreased corneal endothelial cells

2. STUDY OBJECTIVES

The purpose of this clinical study is to demonstrate non-inferiority of DT1MF to AMMF for investigator-graded successful lens centration in Japanese population.

3. INVESTIGATIONAL PRODUCTS

(1) INVESTIGATIONAL PRODUCTS

Commercially available DTMF1 and AMMF products will be used in the study. A brief overview of the two investigational products is shown below.

Name of investigational products	DAILIES TOTAL 1® Multifocal	1-DAY ACUVUE® Moist® (Multifocal)
Approval number	22900BZX00026000	21600BZX00408000
Manufacturing and Distribution company	Alcon Japan Ltd.	Johnson & Johnson K.K. Vision Care Company
SCL IV Group	Group I	Group IV
Material (USAN)	Delefilcon A	etafilcon A
Water content [%]	33	58
Base curve [mm]	8.5	8.4
Diameter [mm]	14.1	14.3
Center thickness [mm] (for -3.00D)	0.09	0.084
Sphere power ranges [D]	-10.00 to -0.25, ±0.00 to +5.00	-9.00 to -0.25, ±0.00 to +5.00
Add power ranges [D]	+1.25D, +2.00D, +2.50D	+1.25D, +1.75D, +2.50D
Preservative solution	Phosphate buffered saline	Boric-acid buffered saline

(2) Usage

Follow each product's direction for use.

(3) Instructions on package and labeling

In accordance with the instructions for commercially available DTMF1 and AMMF products.

In order to keep the subject masked, the blister packages of the investigational products must be put in a seal to conceal the product name from the subjects before dispensing at each study site.

(4) Storage and Management

Commercially available products that are stored and managed by contact lens distributors will be used in this clinical study. The products will not be stored or managed at each study site. The site must get the products prescribed by the investigator, and dispense them with the seal that is described in (3) above. The dispensed study contact lenses will not have to be retrieved even in the case of used or unused. As an exception, DT1MF with any device deficiencies should be retrieved from the subject and returned to the Sponsor if at all possible.

4. SUBJECTS

(1) No. of Subjects

120 subjects required: 1 eye per 1 subject

134 subjects planned

(2) Inclusion Criteria

1) Age 40 or older and must sign the informed consent.
2) Habitual multifocal soft/ silicone hydrogel contact lenses wearers.
3) Requiring a near spectacle ADD of +0.50D to +2.50D (inclusive)
4) Requiring lenses within the power range of the dispensed study contact to be fitted (+5.00 to - 9.00 D).
5) Cylinder if present less than1.00D in either eyes at Visit 1.
6) Vision correctable to 20/30 or 0.2 logMAR or better in each eye at distance.
7) Can be successfully fitted with study lenses at Visit 1, for parameter optimization and fitting.
8) Willing to wear lenses every day or at least for a minimum of ten days in this clinical study for six hours per day, and attend all study visits.

[Rationale for inclusion criteria]

1) and 6): Required per ISO11980: 2012; 4.2.1.1., a)
2) Avoid any adaptation bias for efficacy [redacted] variables.
3) To select subjects who are currently correcting myopia.
4) Study contact lenses must be available for both brands tested.
5) The study products are not designed to correct astigmatism.
7) To represent the normal clinical situation.
8) To ensure that the study contact lenses are the principal correction modality.

(3) Exclusion Criteria

1) Currently wearing DAILIES TOTAL 1® Multifocal or 1-DAY ACUVUE® Moist® Multifocal.
2) Ocular anterior segment infection, inflammation, abnormality, or active disease that would contraindicate contact lens wear.
3) Use of systemic or ocular medications which contact lens wear could be contraindicated as determined by the investigator.

   Subjects using systemic medications that could contribute to dry eye [antihistamines (oral or nasal), antidepressants (oral), retinoids (oral or topical), nonsteroidal anti-inflammatory drugs (topical) and niacin (oral)] may not be enrolled in the study unless they have been on a stable dosing regimen for a minimum of 30 days prior to the study visit.4) Monocular subjects (only one eye with functional vision) or subjects fit with only one lens.
5) Subjects fitted with monovision.
6) Any moderate or severe ocular condition observed during the slit-lamp examination at enrollment visit.
7) Prior refractive surgery (e.g. LASIK, PRK, etc).

8) History of herpetic keratitis, ocular surgery or irregular cornea.
9) A pathological dry eye that precludes contact lens wear.
10) Use of mechanical eyelid therapy or eyelid scrubs within 14 days before Visit 1 and not willing to discontinue during the study.
11) Eye injury or surgery within twelve weeks immediately prior to enrollment for this trial.
12) Enrollment of the investigator or his/her staff, family members of the investigator, family members of the investigator's staff, or individuals living in the households of these individuals.
13) Participation in any clinical trial within 30 days of the enrollment visit.
14) Patient who is judged ineligible as patients in this clinical study by the investigator.

[Rationale for exclusion criteria]
1) and 12): To prevent bias.
2), 3), 7), 9), 11) and 13): As per ISO 11980:2012; 4.2.1.1.b
4) Bilateral wear required.
5) Monovision may affect the quality of vision and could confound efficacy assessments.
6) Abnormal findings would contraindicate lens wear.
8) As per ISO 11980:2012; 4.2.1.1.
10) This may interfere with efficacy assessments.
14) This criterion was established for general safety considerations.

5. STUDY DESIGN

Prospective Multi-Center, Randomized[*1], Single Masked (Subject), Crossover study.

6. STUDY PROCEDURE

(1) Outline

Subjects will be randomly assigned to one of the two sequences of the investigational products (DT1MF and AMMF) and will wear each of the two investigational products in both eyes for at least 11 days each. Randomization manager will create the randomization code for the orders of the investigational product wearing (DT1MF→AMMF or AMMF→DT1MF) at a ratio of 1:1 using the permuted block method. The randomization manager will create the randomization code for the study eye (right or left) and maintain the key code in a masked state [*2], until the time of code breaking.

[*1]: The sequence of study lens use (DT1MF→AMMF, AMMF→DT1MF) is randomized in this study. The subjects wear the same lens in both eyes.
[*2]: The randomization code for sequence of study lens use will be masked only to the subjects. The randomization code for the study eye must be masked for the site, the subjects and sponsor.

(2) Examinations Schedule

Table Examinations Schedule

Procedure/ Assessment		Visit 1		Visit 2[*1]		Visit 3[*1]	Un-scheduled Visit
		Baseline	Disp. CL 1	Follow Up CL 1	Disp. CL 2	Follow up CL 2	
Informed consent		○					
Demographics [Gender, age, habitual multifocal SCL/SHCL (product name, diopter, the average number of hours of wear per day, the average number of days of wear per week)]		○		○[*2]		○[*2]	
Medical history/ Concurrent disease/ Concomitant medications		○		○		○	
Objective refraction		○					
Corneal curvature radius (K value)		○					
Subjective refraction		○					
VA	Best corrected visual acuity with trial frame	○		○		○	[○]
VA	[redacted]						
Biomicroscope: Slit-lamp examination		○[*3]	○	○[*3]	○	○[*3]	[○[*3]]
CL parameter selection		○					[○]
Study lenses dispensing[*4]			○		○		[○]
Lens centration assessment			○	○	○	○	[○]
[redacted]							
Verify inclusion/exclusion criteria		○					
Adverse events, Device Deficiencies		○[*6]	○	○	○	○	○

[○]: To conduct examinations/observations as needed

[*1]: Allowance for next visit: the day after 14 ± 3 days from the present visit.

[*2]: Confirm frequency of Lens 1 or Lens 2 wear (average number of hours per day, number of total days).

[*3]: Including observations of fluorescein corneal and conjunctival staining.

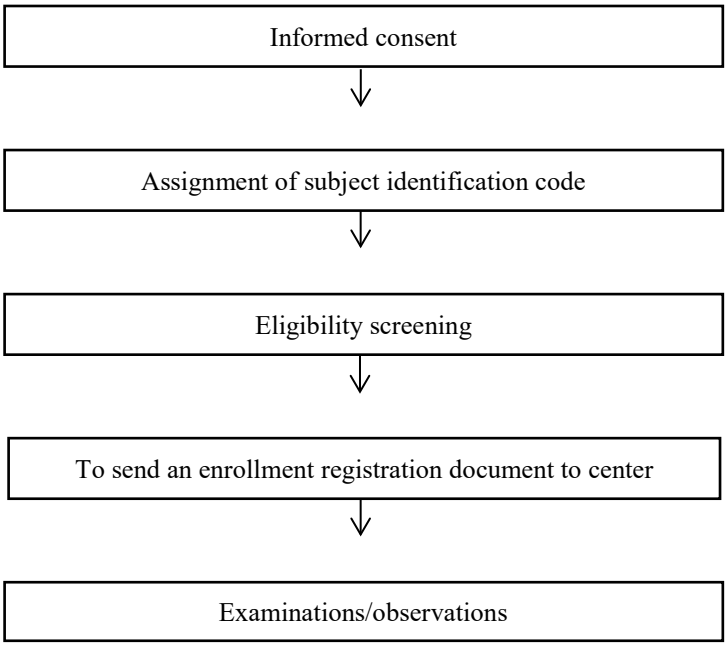
[*4]: Record information of dispensed CL (DT1MF or AMMF) diopter, and lot number.

[redacted]:

[*6]: Document the untoward event that occurred from getting informed consent to the use of the investigational products.

(3) Method of subject enrollment

A flow of subject enrollment is shown below.



1) Subject information and informed consent

After an explanation of the study details is given to a prospective subject, his/her consent to participate in the study will be obtained.

2) Assignment of subject identification code

The subject identification code will be assigned to a subject assessed to be eligible for the study.

3) Eligibility screening

The investigator will assess the eligibility of the subject through examinations and observations needed to assess the eligibility based on the inclusion and exclusion criteria (eligibility screening).

4) Notification to the enrollment registration center

Information of the subject whose eligibility is confirmed will be sent by fax or other means to the registration center. The center will send back the randomization form, which indicates the sequence of contact lens dispensing (DT1MF→AMMF or AMMF→DT1MF).

5) Examinations/observations

Examinations and observations will be performed as specified after Section 6 “Study Procedure”, (4) “Examinations Procedure 2) Visit1: “At dispensing Lens 1”.

(4) Examinations Procedure

To conduct the following examinations at Visit 1, Visit 2 and visit 3. The tests that are generally performed when

prescribing contact lenses can be used as data for clinical study even if such data are from the tests performed before obtaining informed consent. The sequence of the examination procedures can be changed at this clinical study sites. CL parameter selection will be followed each manufacturer's recommended fitting guide.

1) Visit 1: Baseline visit
   [1] After giving a full explanation of the study details to each subject, the investigator will obtain voluntary written informed consent from the subject. The subject identification code will be assigned to a subject assessed to be eligible for the study.
   [2] Collect the information on subject demographics (gender, age, habitual multifocal SCL/SHCL information [brand name, sphere and add powers, average number of hours of wear per day and the average number of days of wear per week]), ocular medical history (up to 12 weeks before informed consent), ocular surgery history, complication, and concomitant medications.
   [3] As subjective questionnaires, provide the subject with "Subject Questionnaire Forms" (for wearing habitual multifocal SCL/SHCL) and collect the forms within a day after the subject completes the questionnaires at the study site.
   [4] Measure binocular VA at 5m, 70cm and 30cm when wearing habitual multifocal SCL/SHCL.
   [5] Perform refractometry and keratometry to measure objective refraction and corneal curvature radius. Perform subjective refraction to measure best corrected visual acuity with an ophthalmoscope.
   [6] Assess fluorescein corneal and conjunctival staining by slit-lamp microscopy according to Section 6-(5) "Evaluation Method" (5) "Corneal staining" and Section6-(5) "Evaluation Method", 6) "Conjunctival staining"
   [7] Select the parameters for investigational product 1 (Lens 1) and investigational product 2 (Lens 2) (lens centration [redacted] assessment (according to Section 6-(5) "Evaluation method" (1) "Lens Centration" [redacted])
   [8] Confirm the presence or absence of adverse events and device deficiencies. If any adverse event and/or device deficiencies is present, record data on the event in the Adverse Event CRF according to Section 10 "Adverse Events and Device Deficiencies, etc." of the protocol. The already existing symptoms and diseases at obtaining informed consent are regarded as complications. The events that are developed anew or aggravated after informed consent are recorded as adverse events.
   [9] If the subject is assessed to be eligible for the study based on these examination results and the inclusion and exclusion criteria, information on the subject will be sent to the registration center by fax or other means.
   [10] Receive the randomization form for the sequence of contact lens dispensing from the registration center by fax or other means.

2) Visit 1: Disp. CL 1
   [1] Observe the ocular anterior segment with Lens 1 by slit-lamp microscopy.
   [2] Assess lens centration [redacted] (10-15 min post insertion) for Lens 1 by slit-lamp microscopy

according to Section 6-(5) “Evaluation Method”, 1) “Lens centration” [redacted]

[redacted]

[3] If any specification adjustment is required, repeat the procedures from [1] to [3] above.

[4] [redacted]

[5] Confirm information on the dispensed Lens 1 (type, diopter and lot number).

[6] Confirm the presence or absence of adverse events and device deficiencies. If any adverse event and/or device deficiencies is present, record data on the event in the Adverse Event CRF according to Section 10 “Adverse Events and Device Deficiencies, etc.” of the protocol.

[7] Schedule the next visit (Visit 2) date. Dispense necessary number of Lens 1 to the subject. Instruct the subject to contact the investigator, etc. if he/she feels any abnormality. If lens has any device deficiencies, let the subject bring it on Visit 2.

3) Visit 2: Follow up CL1

[1] Confirm the time of Lens 1 insertion and the start and end times of examinations on the visit day (and document these times in the medical record).

[2] Confirm the change of concomitant medications, etc.

[3] Confirm whether Lens 1 is used appropriately during the period between the last and present visits (total days of Lens 1 wearing, average of wearing time per day. If subjects visit the clinic without wearing Lens 1, confirm the reason).

[redacted]

[7] Assess lens centration [redacted] for Lens 1 by slit-lamp microscopy according to Section 6-(5) “Evaluation Method”, 1) “Lens centration” [redacted]

[8] Remove Lens 1, and assess fluorescein corneal and conjunctival staining by slit-lamp microscopy according to Section 6-(5) “Evaluation Method” 5)“Corneal staining” and Section6-(5) “Evaluation Method”, 6) “Conjunctival staining”

[9] Measure best corrected visual acuity with trial frame.

[10] Confirm the presence or absence of adverse events and device deficiencies with reference to subjective questionnaire answers. If any adverse event and/or device deficiencies is present, record data on the event in the Adverse Event CRF according to Section 10 “Adverse Events and Device Deficiencies, etc.” of the protocol.

4) Visit 2 Disp. CL 2

[1] Observe the ocular anterior segment with Lens 2 by slit-lamp microscopy.

[2] Assess lens centration [redacted] (10-15 min post insertion) for Lens 2 by slit-lamp microscopy according to Section 6-(5) “Evaluation Method”, 1) “Lens centration” [redacted]

[3] If any replacement in specification is required, repeat the procedures from 1 to 3 above.

[redacted]

[5] Confirm information on the dispensed Lens 2 (type, diopter and lot number).

[6] Confirm the presence or absence of adverse events and device deficiencies. If any adverse event and/or device deficiencies is present, record data on the event in the Adverse Event CRF according to Section 10 “Adverse Events and Device Deficiencies, etc.” of the protocol.

[7] Check the date of the next visit (Visit 3), and tell the subject to bring habitual multifocal SCL/SHCL or glasses when follow up visit. Dispense necessary number of Lens 2 to the subject. Instruct the subject to contact the investigator, etc. if he/she feels any abnormality. If lens has any device deficiencies, let the subject bring it on Visit 2.

5) Visit3: Follow up CL2

[1] Confirming the time of Lens 2 insertion and the start and end times of examinations on the visit day (and document these times in the medical record).

[2] Confirm the change of concomitant medications, etc.

[3] Confirm whether Lens 2 is used appropriately during the period between the last and present visits (total days of Lens 2 wearing, average of wearing time per day). If subjects visit the clinic without wearing Lens 2, confirm the reason.

[redacted]

[7] Assess lens centration [redacted] for Lens 2 by slit-lamp microscopy according to Section 6-(5) “Evaluation Method”, 1) “Lens centration” [redacted]

[8] Remove Lens 2, and assess fluorescein corneal and conjunctival staining by slit-lamp microscopy according to Section 6-(5) “Evaluation Method”, (5) “Corneal staining” and Section6-(5) “Evaluation Method”, (6) “Conjunctival staining”

[9] Measure best corrected visual acuity with trial frame.

[10] Confirm the presence or absence of adverse events and device deficiencies with reference to subjective questionnaire answers. If any adverse event and/or device deficiencies is present, record data on the event in the Adverse Event CRF according to Section 10 “Adverse Events and Device Deficiencies, etc.” of the protocol.

6) Unscheduled Visit (To conduct examinations as needed)

[1] At unscheduled visit resulting from adverse events, etc., confirm the reason for visit and procedures taken during the visit.

[2] Identify the type of the study lens used by the subject.

[3] Perform examinations, assessments, or confirmations considered necessary by the investigator among those listed below:

- Best corrected visual acuity with trial frame
- [redacted]
- Lens centration [redacted]
- Slit-lamp microscopy examination (including sodium fluorescein corneal, etc.).
- Information on the investigational products (diopter and lot number), if changed
- [redacted]

[4] Dispense the required number of the study lens to the subject, as needed.

[5] Confirm the presence or absence of adverse events. If any adverse event is present, confirm the items in the Adverse Event CRF according to Section 10 “Adverse Events and Device Deficiencies, etc.” of the protocol.

(5) Evaluation Method

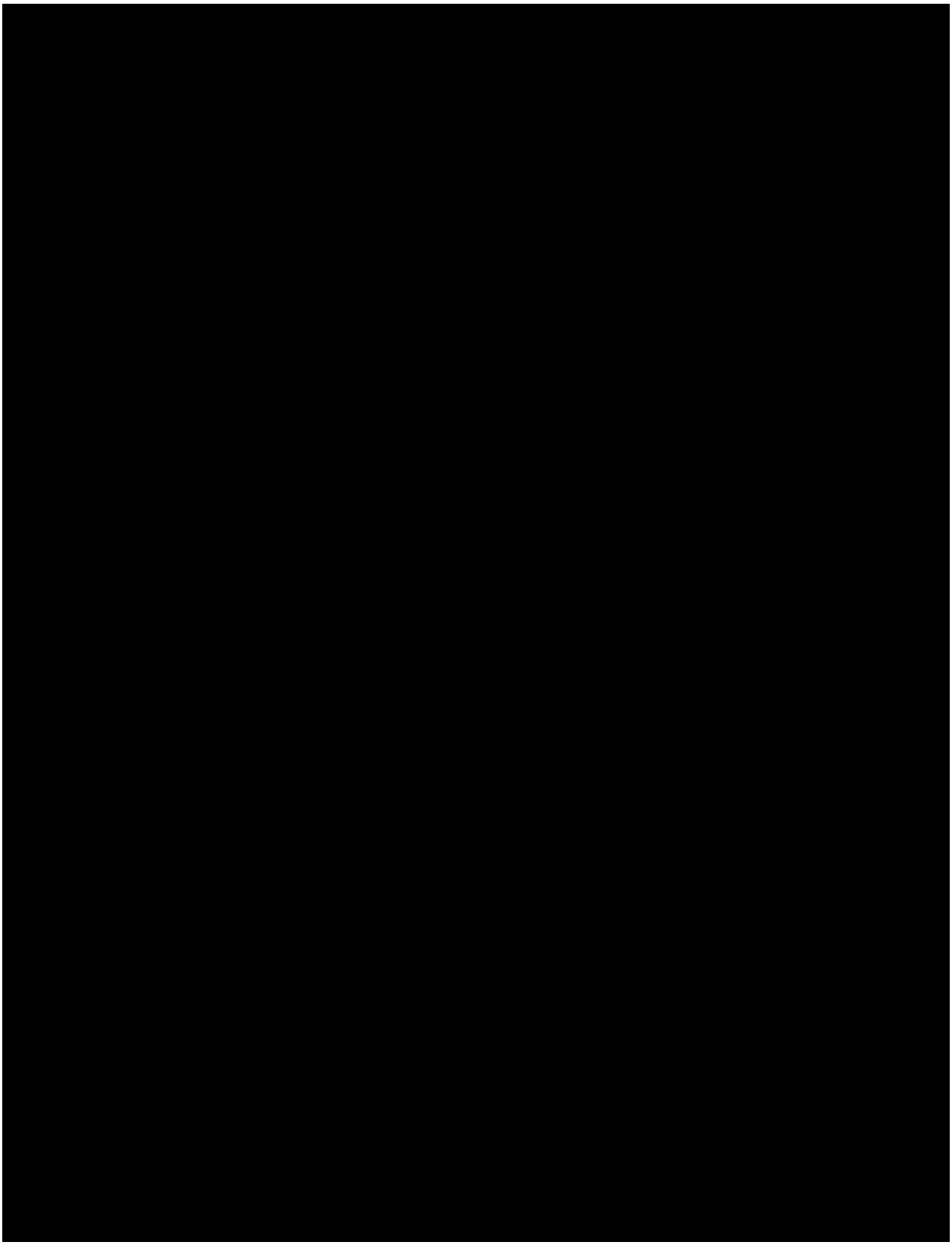
1) Lens centration

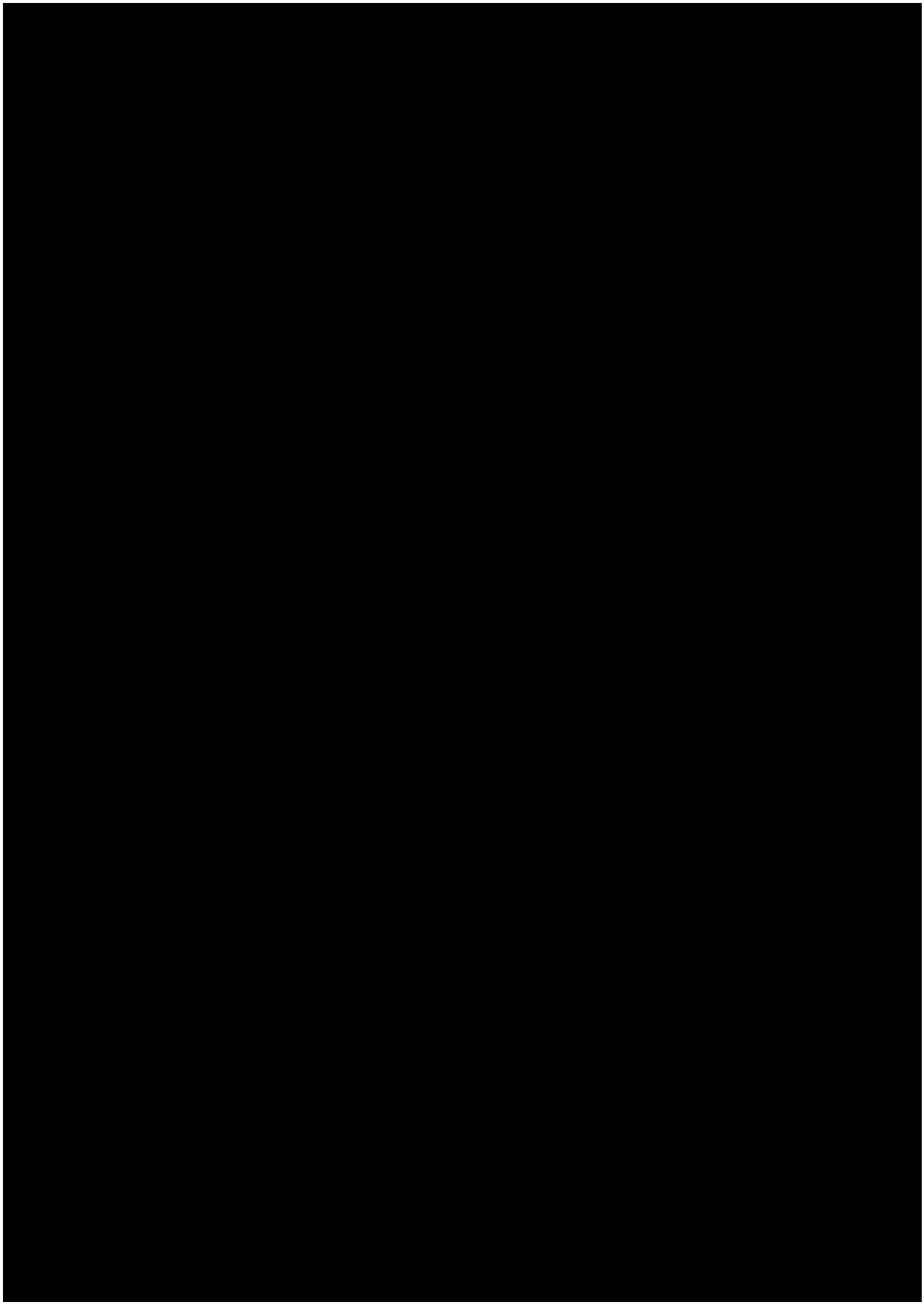
Assess lens centration for each eye by slit-lamp microscopy according to the criteria shown below.

For assessment results other than “Optimal”, check the direction of lens decentration (upward, downward, nasal, or temporal).

	Criteria
0	Centered/ Optimal
1	Slight decentration
2	Mild decentration (without limbal touch)
3	Moderate decentration (with limbal touch but without corneal exposure)
4	Severe decentration (with corneal exposure)

2) [redacted]



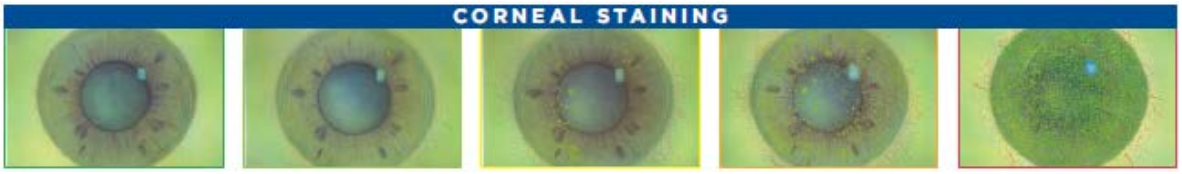


[redacted]

4) Fluorescein corneal and conjunctival staining

Corneal and conjunctival staining with fluorescein of both eyes will be rated by the investigator using a 5 point scale (0= Normal, 1= Trace, 2=Mild, 3=Moderate, 4=Severe).

Corneal staining with fluorescein (EFRON GRADING)



0: Normal 1: Trace 2: Mild 3: Moderate 4: Severe

Conjunctival staining with fluorescein (EFRON GRADING)

0: Normal 1: Trace 2: Mild 3: Moderate 4: Severe

[redacted]

(6) Anticipated study period

From NOVEMBER 2017 to OCTOBER 2018

7. CONCOMITANT THERAPY

(1) Contraindicated drugs

Subjects will be prohibited from using the following drugs and all ophthalmic drugs including over-the-counter products (except artificial tears) during the period from study enrollment through the end of all examinations and observations.

If a subject is administered the following drugs, their dosage and administration must not be changed during the period from study enrollment through the end of all examinations and observations.

Antihistamines (oral or nasal), antidepressants (oral), retinoids (oral or topical), nonsteroidal anti-inflammatory drugs (topical) and niacin (oral).

(2) Contraindicated therapy

Surgical therapies affecting the ocular surface, such as intraocular surgery and ophthalmic laser surgery, are prohibited as concomitant therapies during the study period. Subjects considered requiring these surgical therapies should be withdrawn from the study and be treated appropriately.

8. DISCONTINUED SUBJECTS

(1) Discontinued Subjects

Subjects discontinued the study in the following cases:

1) Upon onset of adverse events which make study continuation difficult.
2) If the investigators judge it necessary to switch the therapy to another
3) The investigators judge to discontinue the study as deviation from inclusion and/or exclusion criteria after using the investigational products which has a problem in safety.
4) Upon cancellation of consent to the study by the subject.
5) Upon request of the subject to discontinue the study.
6) Hospital referral or move of the subject during the study, making it difficult to continue the study.
7) The use of ophthalmic drugs including over-the-counter products (except artificial tears) during the period from study enrollment through the end of all examinations and observations.

8) This was ineligible due to inclusion criteria and exclusion criteria.
9) If the investigators judge it necessary to discontinue the study.

Upon discontinuation of the study, if the investigators decided the examination or observation is necessary, the examination or observation should be carried out as far as possible under the subject's consent, and the date and reason of discontinuation are entered in the case report form.

In case where continuation of the study is difficult because of discontinued visit of the subject to the clinic, the subject is followed over telephone, by mail or other appropriate means and the reason for discontinued visit, survival/death of the subject, presence/absence of adverse events, etc., are entered in the case report form.

(2) Discontinuation of the entire study

If discontinuation of the entire study has become inevitable for reasons of reports on serious safety information from any participating study site or overseas, problems pertaining to the quality of the test articles, and so on, the Sponsor is required to immediately inform the investigator and the head of each study site of discontinuation of the study and its reason in writing.

9. ANALYSIS PLAN

(1) Evaluability

Evaluability of subjects and data will be determined before breaking masked key code and before locking the database lock.

1) Safety

The pre-treatment safety analysis set will include all subjects who consented to participate in the study. The pre-treatment safety analysis set will be the set that will be used to summarize occurrence of adverse experiences prior to exposure to the investigational products except for trial-fit lenses used at Visit 1. The treatment-emergent safety analysis set will include all eyes exposed to any investigational product evaluated in this study except for trial-fit lenses which is used at Visit 1.

2) Full Analysis Set(FAS)

The Full Analysis Set (FAS) includes all randomized subjects who are exposed to any investigational product except for trial-fit lenses which is used at Visit 1 and who complete at least 1 scheduled study visit.

3) Per Protocol Set(PPS)

The Per Protocol Analysis Set (PPS) includes all randomized subjects who are exposed to any investigational product except for trial-fit lenses which is used at Visit 1, who complete at least 1 scheduled study visit and who meet all inclusion criteria and do not meet any exclusion criteria.

The FAS and PPS will be used for primary efficacy analysis in the study. The FAS will be used for main results of primary efficacy analysis. [redacted]. The adverse experiences which occur in the period between informed consent and before exposure to the investigational

products will be analyzed by using data of subjects who consented to participate. The safety analysis after exposure to any investigational product will be performed with the Safety analysis set.

(2) Demographic factors and baseline characteristics

For demographic factors (gender, age [40-49 years,50-59 years, 60-69 years, ≥70 years], type of habitual disposable multifocal SCL/SHCL, ocular medical history, concurrent diseases, and concomitant medications), the number and percentage of subjects will be calculated for all data sets (Safety Analysis Set, FAS, and PPS). For age, diopter of habitual disposable multifocal SCL/SHCL, average number of hours of wear per day and the average number of days of wear per week of habitual disposable multifocal SCL/SHCL, average number of hours of wear per day and total wearing days of investigational products, corneal curvature radius (keratometry), objective refraction (refractometry), subjective refraction (spherical equivalent), best corrected visual acuity with trial frame, and diopter of dispensed lenses, descriptive statistics (arithmetic mean, standard deviation, number of subjects, median, minimum, and maximum) will be calculated.

(3) Efficacy analysis

The primary objective of this study is to demonstrate non-inferiority in investigator-graded successful lens centration of DT1MF to AMMF after 14 ± 3 days of wearing. The primary efficacy analysis will be performed on the right or left eye that is randomly selected as a single study eye.

1) Primary analysis

The primary endpoint of this study is investigator-graded successful lens centration of "Optimal" after 14±3 days of wearing.

[1] Statistical hypotheses

The null hypothesis (H_0) and alternative hypothesis (H_1) for the primary analysis are defined as follows:

$$H_0 : \pi_{(DT1)} - \pi_{(AM)} \leq -10\%$$
$$H_1 : \pi_{(DT1)} - \pi_{(AM)} > -10\%$$

Where $\pi_{(DT1)}$and $\pi_{(AM)}$ denote the percentage of subjects rated as "Optimal" in the DT1MF and AMMF groups, respectively. The 10% is the non-inferiority margin.

[2] Method of analysis

The number and percentage of subjects rated as "Optimal" in investigator-graded lens centration assessment (after 14±3 day of wearing) by each investigational product will be summarized, and a difference between two investigational products will be estimated by using confidence interval based on corresponding binomial test. Non-inferiority of DT1MF to AMMF will be demonstrated in case the lower one-sided 97.5% confidence limit of a difference between investigational lenses lies above -10%. If the crossover effect (DT1MF→AMMF vs AMMF→DT1MF) and/or the period effect (Visit 2 vs. Visit 3) are

found to be significant, DT1MF vs AMMF will be compared at each sequence and/or period separately.

Only if non-inferiority of DT1MF to AMMF is demonstrated, superiority of DT1MF over AMMF will be tested. Superiority will be demonstrated when the lower one-sided 97.5% confidence limit for investigational lens difference lies above 0%. P-value for McNemar test is also calculated. Non-inferiority and superiority hypothetical tests in above are based on the closed testing procedure; no adjustment of significance level for each test will be made.

[redacted]

(4) Handling of missing data

No imputation is planned for missing data.

(5) Multiplicity

Primary analysis will be performed a single variable, and superiority testing will be performed only when non-inferiority testing is demonstrated. [redacted] For defining the sequence of statistical testing in advance, the type I family-wise error (FWE) rate of [redacted] hypothesis tests which include primary efficacy analyses [redacted] is controlled at alpha = 2.5% (one-sided). [redacted]

(6) Safety analysis

The number and percentage of adverse events and adverse experiences which occur in the period between informed consent and before exposure to the investigational products will be presented. For the following variables, observed values and their changes from baseline will be summarized. Continuous variables will be presented descriptive statistics (arithmetic mean, standard deviation, number of subjects, median, minimum, and maximum), whereas categorical variables will be presented the number and percentage.

- Slit-lamp examination
- Best corrected visual acuity with trial frame

(7) Medical economics analysis

No medical economics analysis is planned in the study.

(8) Interim analysis

No interim analysis is planned in the study.

(9) Rationale for the sample size

The sample size was estimated based on a subgroup analysis from a prior clinical study (CLE914-P001 study) in which 54 eyes were from habitual current AMMF wearers. In terms of investigator-graded lens centration after 14±3 days of wearing, a difference was showed that DT1MF had 13.0% better percentage of “Optimal” than AMMF (See the table below).

Table Lens centration assessment by investigator (14±3 days of wearing) (CLE914-P001, Unit: Eye)

		AMMF			Difference between investigational device (DT1MF – AMMF)
		Optimal	Other than Optimal	Total	
DT1MF	Optimal	45	7	52	7
		83.3%	13.0%	96.3%	13. 0%
	Other than Centered/ Optimal	0	2	2	
		0%	3.7%	3.7%	
	Total	45	9	54	
		83.3%	16.7%	100%	

With 120 subjects (one study eye per one subject), the probability that a lower limit of 97.5% one-sided confidence interval of lens difference lies above -10% is more than 99% and the probability of lens difference lying above 0% is 92%, assuming the percentage of "Optimal" in population is the same as in the table above.

[redacted]

[redacted]

[redacted]

As the 120 patients are required for the effectiveness assessment in this study, the 134 patients will be enrolled in order to assume around 10 % discontinuation.

10. ADVERSE EVENTS and DEVICE DEFICIENCIES, etc.

Adverse events will be collected from the time of informed consent even if the investigational product isn't allocated.

(1) General Information

Refer to the Glossary of Terms below for categories of AEs and SAEs.

Adverse Event (AE):

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects after signed informed consent, users or other persons, whether or not related to the investigational medical device (test article). *For subjects, this definition includes events related to the test article or the procedures involved. For users or other persons, this definition is restricted to events related to the test article.*

Serious Adverse Event:

Adverse event that led to any of the following, or that needed treatment not to lead to the following results:

- Death.
- A serious deterioration in the health of the subject that either resulted in:

  a) a life-threatening illness or injury.

  Note: Life-threatening means that the individual was at immediate risk of death from the event as it occurred, ie, it does not include an event which hypothetically might have caused death had it occurred in a more severe form.

  b) any potentially sight-threatening event or permanent impairment to a body structure or a body function.

  c) in-patient hospitalization or prolonged hospitalization.

  Note: Planned hospitalization for a pre-existing condition, without serious deterioration in health, is not considered a serious adverse event. In general, hospitalization signifies that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out- patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.

  d) a congenital anomaly/birth defect,

e) a medically important event or reaction.

Non-serious Adverse Event

Adverse event that does not meet the criteria for a serious adverse event.

Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device (test article).

Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction; and use error or intentional misuse of the test article.

Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Device Deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

Safety Information:

Information about quality, efficacy and safety for medical device and information which is needed for appropriate use, including:

- Use error
- Abnormal Use
- Product tampering
- Product counterfeiting
- Product theft

(2) Procedure for Reporting of serious adverse events (SAE

The investigator will report the serious adverse event or the risk of causing serious adverse event to Alcon within 24 hours after confirming the event.

After obtainment of detailed information on the serious adverse event, the investigator will prepare a report and immediately submit it to Alcon and the head of the medical institutions.

Contact for emergent communication

Alcon Japan Ltd. Clinical Development, CDMA & Regulatory Affairs, Japan.

TEL [redacted] (At night and on holidays: [redacted])

FAX [redacted]

When the SAE is correspond to “Death or a life-threatening ADE” or “Serious and unexpected ADE other than Death or a life-threatening event”, the sponsor will immediately notify them to heads of all medical institutions and all investigators by document.

(3) Report of adverse events and evaluation of the causal relationship

All adverse events (related and unrelated to the medical device) will be documented on the Adverse Event Case Report Form (CRF).

AEs will be sorted into the investigational product by the following periods (Onset time of AE), because this study is cross-over design.

Periods: Onset time of AE	investigational product
Informed consent to Visit 1: baseline	N/A
Visit 1: Dispensing Lens 1 to Visit 2: Follow Up Lens1	Lens 1
Visit 2: Dispensing Lens 2 to Visit 3: Follow Up Lens2	Lens 2

(4) Intensity Assessment of Adverse Events

For every AE, the investigator must assess the intensity (severity). Events should be classified as mild, moderate, or severe. These classifications should be based on the following definitions:

Intensity:

Mild An AE is mild if the subject is aware of but can easily tolerate the sign or symptom.

Moderate An AE is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities.

Severe An AE is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

(5) Follow-up of Subjects / Subjects with Adverse Events

In the event of acknowledging any adverse events, the investigators should immediately take appropriate actions irrespective of the presence or absence of causal relationship with the test article. And the investigators will make a follow-up of the adverse event if it is possible. When the subject needs medical treatment, the investigators should inform the subject of the matter.

For subjects who are experiencing ongoing unresolved adverse events at the time of their study completion or early discontinuation from the study, it is recommended that the investigator schedule an appropriate follow-up visit in order to determine the outcome of the event.

(6) Pregnancy of subjects

Women who is planning to become pregnant during this study period or women who are pregnant at the time of study entry are excluded from participation

(7) Provision of safety information

Investigators provide safety information which is needed to make a detailed report on demand from the sponsor.

11. ETHICS

(1) Ethics committee

Prior to the start of the study, the Independent ethics committee (IEC) of each participating institution is required to inspect and evaluate the planned study as to the acceptability of implementing the study, appropriateness of the contents of the protocol, case report form, questionnaire and informed consent document, and other matters related to the study from the ethical, scientific points of view, with an ultimate goal of protecting the human rights and welfare of the subjects.

The inspection and examination by the IEC may be performed again also during a certain period of time after the start of the study or when the head of the participating institution sees the necessity of additional inspection/examination so that the study may be monitored continuously.

(2) Ethical consideration

The study is implemented after a contract on implementation of the study is concluded between the Sponsor and each participating institution following inspection and authorization of the study by the IEC of each participating institution.

If deemed necessary to ensure safe implementation of the study, the protocol of this study may be revised in accordance with the provisions set forth in “Section 12. PROTOCOL AMENDMENTS”.

This study is carried out in accordance with the principles set forth in the Declaration of Helsinki and the protocol. This study will be conducted in accordance with Good Clinical Practice (GCP) and the Ethical Guidelines for Clinical Studies (2014, Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare Notification No.3, partial revision on 28 February, 2017), in principle.

(3) Protection of subjects’ privacy

To protect the privacy of individual subjects, only identification codes are used to represent the subjects whose data are used in case reports, etc., so that leakage of the identifiable individual information about the subjects can be prevented.

(4) Specifications to secure safety of study subjects

1) Actions to take for adverse events

In the event of acknowledging any adverse events, the investigator or the sub-investigator should immediately take appropriate actions irrespective of the presence or absence of causal relationship with the test article.

2) Supply of new information

In the case of obtaining safety-related new and significant information related to the clinical trial, the sponsor should supply the information in writing to the investigator and the sub-investigator and the head of the study site and take necessary actions.

3) Avoiding emergent risks

In the event of deviating from the study protocol to avoid the emergent risk and secure safety of the study subject or because of other unavoidable clinical reasons, the investigator will retain the record and submit the documentation and justification of the protocol deviation to the sponsor and the head of the study site.

(5) Compensation for health hazards

If any subject has sustained health hazards arising from this study, best healthcare is provided to that subject. The Sponsor needs to be covered by insurance for liability arising from clinical trial.

(6) Payment to subjects

As a reward to the cooperation of each subject with the study, the Sponsor pays an amount of money, predetermined through negotiation with each participating medical institution, to each subject. This payment is not intended to force any subject to remain in the study.

12. PROTOCOL AMENDMENTS

When the protocol, etc. are revised, the sponsor and the investigator will exchange an agreement in writing. The revised protocol, etc. will be reviewed and approved by the IEC of the medical institution before new subjects are enrolled, depending on the necessity.

13. CONSIDERATIONS FOR DOCUMENTATION AND COMPLETION OF CASE REPORT FORM

The investigator, etc. will complete the case report form by himself or herself based on source data in accordance with the protocol and the preparation procedure of the case report form. After preparation of the case report form, he or she will sign and date it, and submit it to the sponsor through the person in charge of monitoring.

The investigator will describe the subjective questionnaires regarding the name of the site and identification code and submit it as a part of CRFs to the sponsor through the person in charge of monitoring.

14. MONITORING

The Sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals. The clinical investigation will be monitored to ensure that:

1. The rights and well-being of the subjects are protected.
2. The reported data are accurate, complete, and verifiable from the source documents.
3. The study is conducted in compliance with the current approved protocol (and amendment[s], if applicable), with current Good Clinical Practices (GCPs), Ethical Guidelines for Clinical Studies and with applicable regulatory requirements, in principle.

The monitor will report the monitoring results to study manager.

15. RETENTION OF THE RECORDS

The following records of this study are properly maintained. Sponsor informs medical institutions when the date to maintain the records has expired.

Medical institutions and investigators shall preserve the protocol, source documents, informed consent forms agreed, informed consent form and other written information, records on GCP and Ethical Guidelines for Clinical Studies (2014, Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare Notification No.3). Above documents excluding medical records should be retained either five years

after the date of completion of the study, or three years after the date of publication/presentation of the final study result whichever date is later. The storage period of clinical record depends on Medical Practitioners Act and other related regulations.

16. CONFIDENTIALITY AND PUBLICATION OF STUDY

All information related to this clinical study including the protocol and therapeutic results are the property of the sponsor, and the investigator and other medical staff engaged in the clinical study must keep such information confidential.

The sponsor can submit the results of this clinical study to the health authority and use the results as "Information on Proper Use" of the product. Sponsor will resister the summary of the study to open database (The Database Center of the National University Hospitals, JAPIC Clinical Trials Information, or JMACCT Clinical Trials Registry, etc.) before conducting the study, and will properly update it based on the revision of the protocol or study progression.

After completion of the study, sponsor and the primary investigators will report the result of the study after taking necessary steps for protecting the rights and benefits of the subjects, related persons, sponsor, investigators, and so on. When publishing the results of this clinical study in the congresses or medical journals, the investigators and other medical staff must pre-inform the sponsor. The sponsor can confirm the contents of presentation beforehand.

17. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

The investigator and the study site must make source data available to the sponsor or the regulatory authority at their request. Such direct access to source data will be performed so that the sponsor or the regulatory authority may confirm whether the clinical study is conducted in accordance with the protocol and whether data of the case report form are indicated accurately.

Regarding the sujective questionnaires, "Subject Questionnaire Forms" is the source data. With reference to Evaluation and Comment of the investigator, etc., there are no source data and they are information directly indicated on the case report form.

18. QUALITY CONTROL AND QUALITY ASSURANCE OF THE STUDY

Quality control and Quality assurance shall be carried out in accordance with GCP standard operational procedures (SOP) and Quality assurance SOP of the Sponsor.

Quality Assurance will evaluate that the study is properly conducted according to the protocol, Standard Operation Procedures of Medical Affairs/ Clinical Development Group / Clinical Biometrics, GCP and Ethical Guidelines for Clinical Studies (2014, Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare Notification No.3).

19. OBLIGATIONS OF INVESTIGATORS

Selection of Trial Subjects

In the selection of trial subjects, investigator(s) and sub-investigators shall, from the standpoint of human rights

and on the basis of the standards for selection and exclusion set forth in the trial protocol(s), carefully consider whether to request participation in the trial, taking into consideration such factors as the subject's general state of health, symptoms, age, gender, capacity to consent, dependency on investigator(s), etc., and participation in other trials.

Obtaining Consent of Subjects

Investigator(s) and sub-investigators shall obtain consent for the subject to participate in the trial from the subject or legally acceptable representative thereof, in accordance with GCP.

Medical Treatment of Subjects

The investigator shall have the responsibility for all decisions on medical treatment relating to the trial.

The director of the institution and the investigator shall ensure that the subject is provided with adequate medical treatment for all trial-related adverse events that constitute clinical problems during and after the subject's participation in the trial. Further, when an investigator or sub-investigator becomes aware of the need for medical treatment of an adverse event, he or she shall so inform the subject.

The investigator or sub-investigator shall confirm whether the subject has another attending physician, and with the consent of the subject, inform the attending physician of trial participation.

If a subject desires to withdraw or withdraws participation during the trial, the subject is not obliged to clarify the reason for withdrawal, but the investigator or sub-investigator shall make appropriate efforts, based on full respect for the rights of the subject, to determine the reason.

Agreement on and Compliance with Trial Protocol(s)

Prior to reaching an agreement with the sponsor on the trial protocol(s) and case report forms (CRF), the investigator shall confer with the sponsor on the basis of the trial protocol(s), and other required materials and information submitted by the sponsor, and shall give full consideration to the ethical and scientific suitability of conducting the trial. The same shall apply if the trial protocol(s) is revised.

The investigator shall reach agreement with sponsor on the content of the trial protocol(s), and as evidence of agreement to comply with the trial protocol(s), the investigator and sponsor shall date and affix their signatures or personal seals to a trial protocol(s) or alternative document. The same shall apply if the trial protocol(s) is revised, or if, due to a directive of the director of the institution based on the opinion the IEC, the trial protocol(s) is corrected.

Submission of Documents to the IEC

Before and during the trial period, the investigator(s) shall keep current those documents that are subject to review by the IEC and are to be submitted by the investigator(s). If these documents are augmented, updates or revised, all must be submitted promptly to the director of the institution.

Directive and Decisions of the Director of the Study site

When the IEC gives its approval to conduct the trial on condition of certain revisions, and the investigator has been informed in writing of the directives and decisions of the director of the institution based thereon, the

investigator shall commence the trial in accordance with these directives and decisions.

When the IEC gives its approval to continue a trial in progress or to continue a trial on condition of certain revisions, and the investigator has been informed in writing of the directives and decisions of the director of the institution based thereon, the investigator shall continue the trial in accordance with these directives and decisions.

When the IEC cancels its approval to an item related to a trial in progress (including its termination or suspension) and the investigator has been informed in writing of the directives and decisions if the director of the institution based thereon, the investigator shall comply with these directives and decisions.

Use, etc., of the investigational product(s)

The investigator shall ensure that the investigational product(s) are used only in accordance with methods that comply with the approved trial protocol(s).

Deviations etc. from Trial Protocol(s)

The investigator or sub-investigator shall not undertake any deviation from or modification of the trial protocol(s) without prior written agreement between the investigator and the sponsor and written approval based on prior inspection by the IEC. This is not, however, applicable in the case of changes related solely to cases that are medically unavoidable in order to avoid imminent danger to the subject, or in the case of management matters (e.g., a change in telephone number).

The investigator or sub-investigator shall keep a record of all actions deviating from the trial protocol(s).

The investigator or sub-investigator shall prepare a record describing the reason(s) etc. therefore, submit the record regarding deviation to the sponsor in order to avoid imminent danger to the subject, and retain a copy.

The investigator or sub-investigator may deviate or change the protocol without prior consent in writing with the sponsor or a prior approval from IEC for medically unavoidable reasons in order to avoid imminent danger to the subject. In this case, the investigator shall obtain approval for the deviation and change by submitting the contents and the reason of the deviation and change and the plan if the revision in the Protocol is appropriate to the Sponsor, the head of the medical institution and IEC via the head of the medical institution as promptly as reasonably possible, and obtain approval from the head of the medical institution and agreement from the sponsor via the head of the medical institution.

Recording and Reporting the CRF

The investigator or sub-investigator shall prepare CRFs and subjective questionnaires in accordance with the trial protocol(s), affix thereto his or her signature or personal seal, and submit them to the sponsor. The investigator shall retain copies of the CRFs and subjective questionnaires submitted.

The investigator shall inspect CRFs prepared by sub-investigators prior to their submission to the sponsor, and upon confirming that there is no problem, affix thereto his or her signature or personal seal. The investigator shall also inspect modifications or revisions to CRFs undertaken by sub-investigators, and confirm that there is no problem.

The investigator shall ensure that the data in the CRFs and all other documents submitted to the sponsor are accurate, complete, legible, and submitted in a timely manner, and that a subject identification code is used for

identifying subjects.

Data in the CRFs that are based on original materials shall not conflict with the original materials. When there is any discrepancy with the original, the investigator shall prepare a record explaining the reason therefore, submit it to the sponsor, and retain a copy.

In modifying or correcting CRFs, the investigator shall follow the manual provided by the sponsor. If there is any modification or correction whatever in a CRF, it must be dated and the signature or personal seal affixed. An explanation of the change must be provided if the change is critical. Further, the modification or correcting shall not be such as to render the initial writing unclear (i.e., an audit trail shall be maintained).

The investigator should submit records of modification and correction of the case report form to the Sponsor and retain a photocopy of each record.

Reports, etc. in the Course of the Trial

In order to be available for ongoing review by the IEC, the investigator shall submit a written overview of the status of the trial to the director of the institution annually, or more frequently when requested by the IEC.

With respect to any trial modification that could have a significant effect on the conduct of the trial or could increase the risk to subjects, the investigator shall promptly submit a written report to the sponsor, the director of the institution and, via the director of the institution, to the IEC.

Except in cases in which the trial protocol(s), etc. provide that urgent notification is not required, the investigator shall notify the sponsor promptly of all serious adverse events. After the urgent notification, a detailed written report shall be made in due course.

With respect to adverse events that are specified in the trial protocol(s) as serious for evaluation of the safety of the investigational product(s), the investigator shall report to the sponsor, observing the reporting requirements and deadlines set forth in the trial protocol(s).

The investigator shall report all serious adverse events to the director of the institution promptly and in writing.

With respect to serious adverse events or serious adverse device effects, including cases of death, the investigator shall submit to the sponsor, director of the institution or IEC any additional information (autopsy reports, final treatment records or other requisite information that they may request).

Termination or Suspension of the Trial

When for any reason the trial is terminated or suspended, the investigator shall notify the subjects promptly to that effect, and shall ensure that subjects receive appropriate medical treatment and post-treatment.

When the investigator terminates or suspends the trial, the investigator shall notify the director of the institution promptly and in writing to that effect, and shall provide a detailed written explanation for the termination or suspension.

Completion of the Trial

When the trial is completed, the investigator shall notify the director of the institution in writing to that effect, and report in writing an overview of the trial results.

Storage of Records

The investigator shall retain essential documentation relating to the conduct of the trial in accordance with the directives of the director of the institution.

20. INFORMED CONSENT

Time to Obtain Consent

The investigator or sub-investigator will obtain written consent by the trial subject prior to the commencement of the study.

Methods for Explaining to Trial Subjects

The investigator (or sub-investigator) will give explanations to trial subjects. Study collaborators can give supplemental explanations.

The explanations should be given based on the explanation/consent document using terms which are the easiest to understand (non-technical terms). Questions made by trial subjects should be answered appropriately in the way the trial subjects can understand.

Methods for Obtaining Consent

(1) The investigator (or sub-investigator) who has given explanations will sign and date the consent document.
(2) If any study collaborator has given supplemental explanations, the study collaborator will also sign and date the consent document. (Study collaborators are not allowed to solely give all necessary explanations to trial subjects.)
(3) Supply the trial subject with the consent document and explanation document describing aforementioned necessary information and take sufficient time for the trial subject to decide whether or not he/she should participate in the clinical study.
(4) Before obtaining consent, take sufficient time for the trial subject to sufficiently review the consent items and ask any questions. Answer the questions in a convincing manner.
(5) Obtain the trial subject's spontaneous written consent to participate in the clinical study.
(6) After obtaining the consent document signed and dated by the trial subject, the investigator (or sub-investigator) will enter the date of consent in the CRF and in the medical record. All consent documents must be retained.
(7) Supply the trial subject with the copy (duplicate for the trial subject) of the consent document and the explanation document before the trial subject participates in the clinical study.
(8) If the explanation document or consent document is subject to revision during the participation of the trial subject, follow the above procedures and re-obtain consent.

Items Mentioned for the Written Informed Consent Form and Explanatory Documents

(1) The fact that the clinical study involves research.
(2) The purpose of the trial.
(3) The name and title of the investigator or sub-investigator, and how he or she can be contacted.
(4) The trial method (including the aspects of the trial that are experimental, subject’s inclusion/exclusion criteria,

and when the trial is randomized, the probability of randomization for each treatment).

(5) The expected clinical benefits, and the foreseeable risks or inconveniences to the subjects. (If any benefits for the subject will not be expected, it must be informed to the subject.)

(6) When the persons to be enrolled as trial subjects are subjects, the availability of other medical treatments for their condition, and the potential major benefits and risks of such treatments as are available.

(7) The expected duration of the subjects' participation in the trial.

(8) Subjects may deny or withdraw their will to participate in a clinical study at any time since participation in a clinical study is voluntary. Subjects will not be treated disadvantageously for denying or withdrawing participation, nor will not lose their due benefit for not participating in the clinical study.

(9) Handling of investigational products in case of withdrawing from the clinical study.

(10) The monitor, auditor, Ethics committee etc., and the regulatory authority may view the original information related to the medicine. In such a case, the confidentiality of the subject is protected. The subject approves the viewing of such information by signature and seal or signature in the informed consent.

(11) That the subjects' confidentiality will be protected even when the results of the clinical study are published.

(12) The person in the study site whom the subjects should contact for further information about the trial or their rights, or if they develop a health problem associated with the trial.

(13) The compensation and medical treatment the trial subjects can receive should they develop a health problem associated with the trial.

(14) The number of subjects expected to be enrolled in the trial (including discrete variable).

(15) If information is received that may affect the will of the subjects regarding the subjects' ongoing participation in the trial, that information will be passed on promptly to the subjects.

(16) The circumstances under which or the reasons subjects will be withdrawn from the trial.

(17) The specifics about any expense the trial subjects will have to pay.

(18) The specifics about any cash or the like that will be paid to the trial subjects (including the arrangement for calculating the sum to be paid).

(19) Responsibilities of the trial subjects.

(20) Information about Independent ethics committee (IEC)

(21) The name of the study and the fact that the head of medical institute approved the conduct of the study

(22) The procedure of disclosure of information

(23) The fact that the documents related to protocol and procedure of the study are available, as far as there is no interruption regarding protection of personal information and originality of the study, depending on the request from subject etc. Also procedure of its access.

(24) Handling of personal information (including the procedure of anonymity, if applicable)

(25) The procedure of storing and disposal of the information

(26) Conflict of Interest of the investigator, medical institution etc. regarding the study, including funding source, personal income and so on.

(27) If there is a possibility that the sample or information of subjects might be used in future study or provided to other research institution, the fact and assumed contents when informed consent is obtained.

Revision of Informed Consent Form and Explanatory Documents

If the investigator acknowledges the necessity of revising the explanatory document used for obtaining consent, in the case of the obtainment of the information which may affect the trial subject's intention to continuously participate in the clinical study or in other cases, immediately revise the explanatory document and have the revision approved by the IEC.

21. CONFLICT OF INTEREST

Alcon Japan Ltd. is sponsor of this clinical study. Alcon Japan Ltd. and head of the medical institution will sign a contract for the clinical study. Financial cost of the study will be sponsored by Alcon Japan Ltd in accordance with the contract.

Financial information to medical institutions paid by Alcon Japan Ltd. is disclosed at Homepage of Alcon Japan Ltd..

22. REFERENCES

1) Compan V, Lopez-Alemany A, Riande E, *et al.* Biological oxygen apparent transmissibility of hydrogel contact lenses with and without organosilicon moieties. *Biomaterials* 2004; 25: 359–365.

2) NEGISHI Kazuno, Way to cope with presbyopia, Journal of the Eye 2010; 27: 751-756.

3) Legras R, Benard Y, Rouger H. Through-focus visual performance measurements and predictions with multifocal contact lenses. *Vision Res* 2010; 50: 1185-1193.

4) Dumbleton K, Woods CA, Jones LW et al. The impact of contemporary contact lenses on contact lens discontinuation. *Eye Contact Lens* 2013; 39: 93-99.

5) Varikooty J, Keir N, Richter D et al. Comfort response of three silicone hydrogel daily disposable contact lenses. *Optom Vis Sci* 2013; 90: 945-953.

6) HOSAKA Koichi, Product introduction, Multifocal 2 week daily disposable silicone hydrogel contact lenses “Air Optix Multifocal”. Journal of Japan Contact Lens Society 2009; 51: 309-312.

7) Guillon M, Maissa C, Cooper P et al. Visual performance of a multi-zone bifocal and a progressive multifocal contact lens. *CLAO J* 2002; 28: 88-93.

8) MARUYAMA Kunio, The 36th product introduction, 1-Day ACUVUE® MOIST® ***Multifocal.*** Journal of Japan Contact Lens Society 2015; 57: 289-293.

Signature page

The Sponsor and the Principal Investigator agree to conduct the study in accordance with the details and procedures described in this study protocol.

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Principal Investigator

Medical Institution: [_____]

Affiliation and position: [_____]

Name (Signature): [_____]

(Signature)

Date: _____

Sponsor

Director, Clinical Development, Alcon Japan, Ltd.

Name (Signature): [_____]

(Signature)

Date: _____