Short Title:

Statistical Analysis Plan
CLJ369-P001

Full Title:

Statistical Analysis Plan
CLJ369-P001 /
NCT03341923

Protocol Title:	Clinical evaluation of DAILIES TOTAL1® Multifocal compared to 1-Day Acuvue® Moist® Multifocal in a Japanese population.
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Author:	[redacted] [redacted], Japan
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Job Notes:	

This is the original (Version 1.0) Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 1.0 of the study protocol.

Executive Summary:

Key Objectives:

The objective of this study is to demonstrate non-inferiority of DAILIES TOTAL1® Multifocal (DT1MF) to 1-DAY ACUVUE® Moist® Multifocal (AMMF) for Investigator-graded successful lens centration in Japanese population.

Decision Criteria for Study Success:

Primary Efficacy

Non-inferiority of DT1MF to AMMF will be demonstrated for Investigator-graded lens centration of "Optimal" after 14 days of wear with a non-inferiority margin of 10%.

[redacted]

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1 Study Objectives and Design

1.1 Study Objectives

The objective of this study is to demonstrate non-inferiority of DAILIES TOTAL1® Multifocal (DT1MF) to 1-DAY ACUVUE® Moist® Multifocal (AMMF) for Investigator-graded successful lens centration in Japanese population.

1.2 Study Description

This is a prospective, multi-center, single masked (subject), randomized[1] and crossover study. Subjects will be randomly assigned to one of the two orders of the investigational product wearing (DT1MF to AMMF or AMMF to DT1MF) at a ratio of 1:1 using the permuted block randomization. Subjects will wear each study article (DT1MF and AMMF) in both eyes for at least 11 days each. The randomization manager will also 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.

The subject who wears habitual presbyopic soft/silicone hydrogel contact lens (multifocal lenses only) with a near spectacle ADD of +0.50D to +2.50D (inclusive) will be enrolled. The subjects will wear each of the investigational products for 14±3 days. During the observation period, the subjects remove and discard the lenses every night and use a new pair of lenses every morning. As 120 patients are required for the effectiveness assessment in this study, 134 patients will be enrolled assuming around ten percent discontinuation. One eligible eye for effectiveness analysis will be randomly selected as a study eye according to the permuted block randomization. Scheduled Visits are listed in Table 1-1, as follows.

Table 1-1 Schedule of Study Visit

Days from Dispensing		Study Visit
Visit 1	Pre-Dispensing	Visit 1: Baseline Visit
	Dispensing CL1	Visit 1: Dispensing CL1
Visit 2	14 ± 3 Days after dispensing CL1	Visit 2: Follow up CL1
	Dispensing CL2	Visit 2: Dispensing CL2
Visit 3	14 ± 3 Days after dispensing CL2	Visit 3: Follow up CL2

[1] The sequence of study lens use (DT1MF to AMMF or AMMF to 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 target eye must be masked for the site, the subjects and sponsor.

1.3 Randomization

Subjects will be randomly assigned to one of the two orders of the investigational product wearing (DT1MF to AMMF or AMMF to DT1MF) at a ratio of 1:1 by using the permuted block randomization. Study eye (right or left) will also be randomly determined by using the permuted block randomization.

1.4 Masking

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 to the sites, the subjects and sponsor.

1.5 Interim Analysis

No interim analyses are planned for this study.

2 Analysis Sets

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

2.1 Efficacy Analysis Sets

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.

Per Protocol Analysis 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 do not meet any of the critical deviation or evaluability criteria identified in the Deviations and Evaluability Plan (DEP).

The FAS and the PPS will be used for primary effectiveness analysis in this study. The FAS will be used for main interpretation of primary effectiveness results. [redacted]

2.2 Safety Analysis Set

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. 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.

2.3 Pharmacokinetic Analysis Set

Not Applicable.

3 Subject Characteristics and Study Conduct Summaries

For demographic factors (gender, age [40-49 years,50-59 years, 60-69 years, ≥70 years], type of habitual 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 multifocal SCL/SHCL, average number of hours of wear per day and the average number of days of wear per week of habitual 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.

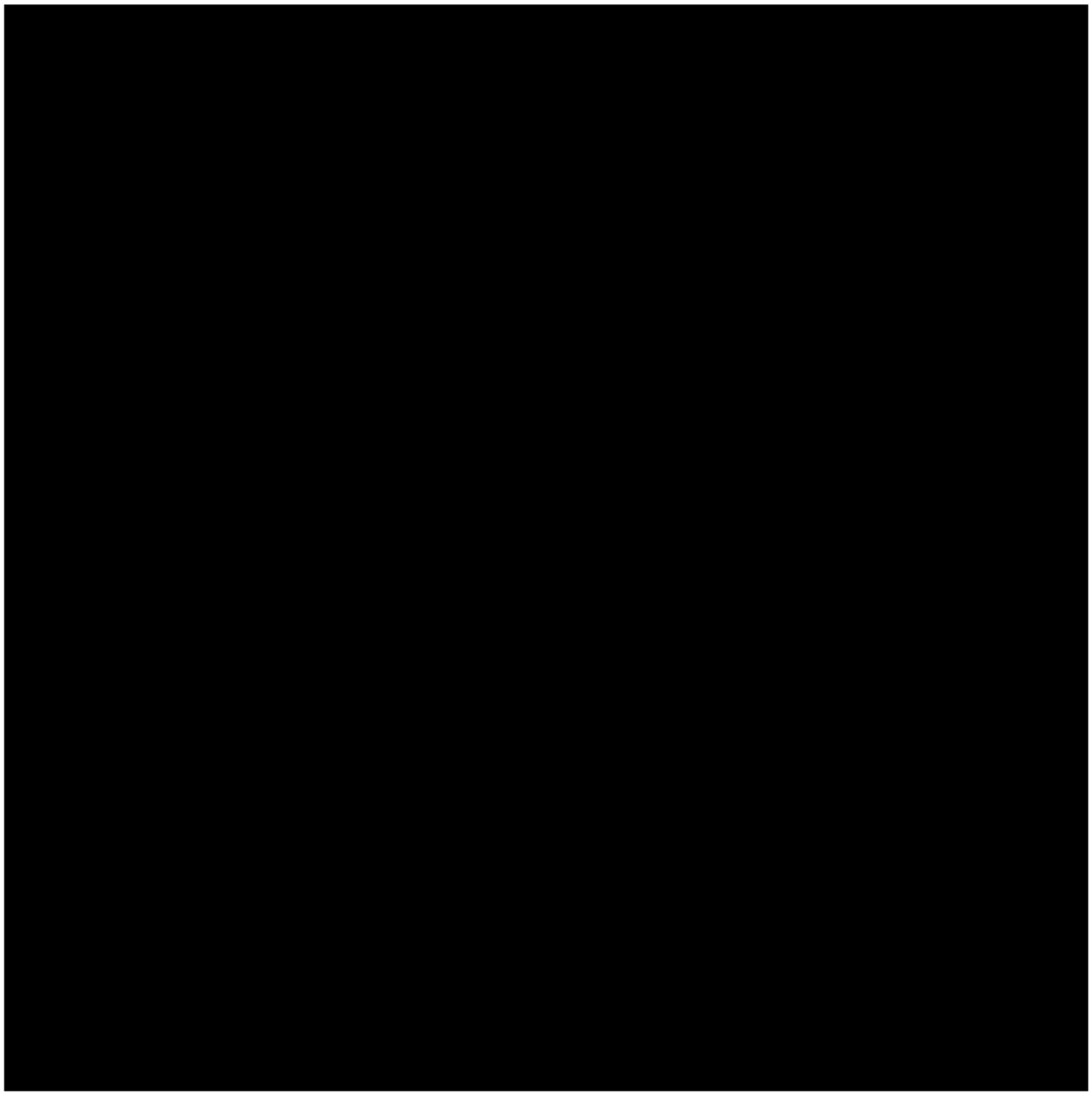
4 Efficacy Analysis Strategy

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 effectiveness analysis will be performed on the right or left eye that is randomly selected as a single study eye.

4.1 Efficacy Endpoints

Primary effectiveness variable is as follow.

- Investigator-graded successful lens centration of "Optimal" after 14±3 days of wearing.



4.2 Efficacy Hypotheses

The primary endpoint of this study is investigator-graded successful lens centration of "Optimal" after 14±3 days of wearing. The population proportion and numbers are tabulated in Table 4-1.

Table 4-1 Paired Data for Crossover Study

		AMMF		Total
		Optimal	Non-Optimal	
DT1MF	Optimal	*e* *(π1)*	*f* *(π2)*	*e+f* *(π1+ π2)*
	Non-Optimal	*g* *(π3)*	*h* *(π4)*	*g+h* *(π3+ π4)*
Total		*e+g* *(π1+ π3)*	*f+h* *(π2+ π4)*	*n*

e+f+g+h = n, π1+ π2+ π3+ π4 = 1.
The π. indicates the population proportion for each cell.

The null hypothesis (H0) and alternative hypothesis (H1) for the primary analysis are defined as follows:

$$H_0 \quad \pi(DT1MF) - \pi(AMMF) \leq -10\%$$
$$H_1 \quad \pi(DT1MF) - \pi(AMMF) > -10\%$$

, where $\pi(DT1MF)$ and $\pi(AMMF)$ represent the population proportion of subjects rated as "Optimal" in the DT1MF and AMMF groups, respectively. $\pi(DT1MF) = \pi1 + \pi2$ and $\pi(AMMF) = \pi1 + \pi3$. Population treatment difference; $\pi(DT1MF) - \pi(AMMF) = (\pi1 + \pi2) - (\pi1 + \pi3) = \pi2 - \pi3$. The value of 10% is used as the non-inferiority margin.

Treatment proportion difference ($\hat{\theta}$) will be

$$\hat{\theta} = \frac{e+f}{n} - \frac{e+g}{n} = \frac{(f-g)}{n}$$

, and its asymptotic lower one-sided 97.5% confidence limit will be calculated as follows (Unmodified Wald method [Newcomb, R. G., 1998]).

$$\hat{\theta} - 1.96 \times SE$$

, where $SE = \{\sqrt{f+g-(f-g)^2/n}\}/n$.

4.3 Statistical Methods for Efficacy Analyses

4.3.1 Primary Effectiveness Analysis

The primary effectiveness objective of this study is to demonstrate non-inferiority of DT1MF to AMMF for investigator-graded successful lens centration after 14±3 days of wearing, more specifically, non-inferiority of DT1MF to AMMF will be demonstrated in case the lower one-sided 97.5% confidence limit of a treatment proportion difference lies above -10%.

If and only if non-inferiority is demonstrated, superiority of DT1MF over AMMF in Investigator-graded lens centration of "Optimal" will be tested. The superiority of DT1MF to AMMF will be demonstrated when a 97.5% one-sided lower confidence limit of lens difference lies above 0%.

If the Sequence (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 period and/or sequence separately.

Period Effect and Sequence Effect (Crossover Effect) will be investigated with the three-way table classifying four types of response by each sequence group (Table 4-3).

Table 4-2 Analysis of Period Effect and Sequence Effect for Crossover Study

Sequence Group	Period Effect		Sub Total	Sequence Effect		Sub Total	Total
	DT1MF Optimal & AMMF Non-Optimal	DT1MF Non-Optimal & AMMF Optimal		DT1MF Optimal & AMMF Optimal	DT1MF Non-Optimal & AMMF Non-Optimal		
DT1MF→AMMF	n111	n112	n11.	n211	n212	n21.	n.1.
AMMF→DT1MF	n121	n122	n12.	n221	n222	n22.	n.2.
p-value*	0.xxxx		n1..	0.xxxx		n2..	n

*Fisher's Exact Test

If there were Period Effect and both sequence groups had propensity to have more "Optimal" in the second period, the proportion of n112 and n121 should be larger. Or, if there were Period Effect and both sequence groups had propensity to have less "Optimal" the second period, the proportion of n111 and n122 should be larger (Mainland-Gart) [2], [3], [4].

On the other hand, if there were Sequence Effect that DT1MF had propensity to have more "Optimal" in the first period and AMMF had propensity to have more "Optimal" in the second period, the proportion of n211 and n222 should be larger. Or, if there were Sequence Effect and DT1MF had propensity to have more "Optimal" in the second period and AMMF

had propensity to have more "Optimal" in the first period, the proportion of n212 and n221 should be larger (Hills-Armitage) [2], [5].

Fisher's exact test will be performed to add statistical insight in addition to descriptive statistics, although the statistical power might not be necessarily maintained due to insufficient sample size.

[redacted]

Table 4-4 summarizes the key effectiveness analyses.

Table 4-4 Summary of Analysis Strategy for Primary [redacted] Efficacy Endpoints

Endpoint	Main vs. Sensitivity Approach[a]	Statistical Method[b]	Analysis Set	Missing Data Approach
Primary				
Investigator-graded successful lens centration after 14±3 days of wearing	M	Unmodified Wald method	FAS (Study Eye)	Observed data only
Investigator-graded successful lens centration after 14±3 days of wearing	S	Unmodified Wald method	PPS (Study Eye)	Observed data only
Investigator-graded successful lens centration after 14±3 days of wearing	S	Unmodified Wald method	FAS (Non-Study Eye)	Observed data only
[redacted]				

[a]M=Main analysis approach; S=Sensitivity analysis approach
[b]Further details on statistical models are:
[redacted]

[redacted]

4.4 Multiplicity Strategy

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

4.5 Subgroup Analyses and Effect of Baseline Factors

Subgroup analyses of the primary endpoint will be conducted to assess the consistency of treatment effect across various subgroups.

The consistency of the treatment effect of the primary endpoints will be assessed descriptively using summary statistics by category of the following subgroup factors:

- Age category (<60, 60-69, 70-79, ≥80 years),
- Sex (Female, Male)
- Investigator

4.6 Interim Analysis for Efficacy

No interim analysis is planned.

5 Safety Analysis Strategy

5.1 Safety Endpoints

The safety endpoints are as follows.

- Biomicroscopy findings: Slit-lamp examination
- Best corrected visual acuity with trial frame
- Adverse events
- Device deficiencies

5.2 Safety Hypotheses

There are no formal safety hypotheses in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of safety endpoints listed in Section 5.1.

5.3 Statistical Methods for Safety Analyses

The analysis set for all safety analyses is defined in Section 2.2. Safety variables after exposure to the test article are listed in Section 5.1. Each safety variable will be summarized descriptively.

5.3.1 Biomicroscopy findings: Slit-lamp examination

Number and percentage of presence or not presence of biomicroscopy finding will be tabulated by each investigational product and by visit. For each visit, a frequency and incidence table of the clinical diagnoses identified as biomicroscopy findings will be presented by each investigational product. Clinical diagnoses will be coded and analyzed using MedDRA.

5.3.2 Best corrected visual acuity with trial frames

For best corrected decimal visual acuity with trial frame, descriptive statistics (mean, mean ± dispersion factors (DF), N, median, min and max) will be provided.

In order to compute the mean of decimal visual acuity correctly, the geometric mean must be used for uncorrected distance visual acuity and best corrected distance visual acuity.

The formulas for transforming from decimal acuity to logMAR score and back are as follows.

$$\textbf{LogMAR} = -\text{Log}_{10}\ \textbf{(Decimal Acuity)}$$

$$\textbf{Decimal Acuity} = \text{antiLog}\ (-\textbf{LogMAR}) = 10^{-\textbf{LogMAR}}$$

For reference, the mean of decimal acuity is defined as follows.

$$\textbf{Mean of Decimal Acuity} = 10^{\textbf{mean of (-Log MAR)}} = 10^{\textbf{mean of Log10 (Decimal Acuity)}}$$

For geometric means, dispersion factors (DF) corresponds to standard deviations and defined as:

$$+DF = 10^{(\text{mean of Log10 (Decimal Acuity)} + \text{Log (SD)})} - 10^{\text{mean of Log10 (Decimal Acuity)}}$$

$$-DF = 10^{(\text{mean of Log10 (Decimal Acuity)})} - 10^{(\text{mean of Log10 (Decimal Acuity)} - \text{Log (SD)})}$$

where, Log (SD) is a standard deviation of Log_{10} (Decimal Acuity).

The number and percentage of eyes with best corrected visual acuity decrease from the dispending visit to the follow-up visit will be presented by each investigational product.

5.3.3 Adverse Events

The number and percentage of eyes with ocular adverse events will be presented by each investigational product. Also, the number and percentage of subjects with non-ocular adverse events will be presented by investigational product. An eye with multiple ocular AEs of the same preferred term is only counted once toward the total of this preferred term. Also, a subject with multiple non-ocular AEs of the same preferred term is only counted once toward the total of this preferred term.

Adverse events will be summarized in the following tables:

- All Adverse Events (Serious and Non-Serious Combined)
  - Ocular
  - Non-Ocular
- All Adverse Device Effects
  - Ocular
  - Non-Ocular
- All Serious Adverse Events (including Serious Adverse Device Effects)
  - Ocular
  - Non-Ocular

Also, patient listings will be included for adverse experiences occurred prior to exposure to the study lenses with pre-treatment safety analysis set.

5.3.4 Device Deficiencies

A patient listing will be provided for the device deficiencies.

5.4 Interim Analysis for Safety

No interim analysis is planned.

6 Pharmacokinetic Analysis Strategy

Not Applicable.

7 Analysis Strategy for Other Endpoints

Not Applicable

8 Sample Size and Power Calculations

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 Table 8-1 below).

Table 8-1 Investigator-Graded Lens Centration after 14±3 Days of Wearing

		AMMF			Difference (DT1MF – AMMF)
		Optimal	Other	Total	
DT1MF	Optimal	45	7	52	7
		83.3%	13.0%	96.3%	13. 0%
	Other	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]

[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.

9 References

[1] Newcomb, R. G., "Improved Confidence Intervals for the difference between binomial proportions based on paired data," *Statistics in Medicine,* vol. 17, p. 2635-2650, 1998.

[2] Yamaguchi Y., "Two types of the effects of order of questions - effect of position and interaction effect between position and question -," Paper collection No. 52 of School of Sociology, Bukkyo University. (in Japanese), March 2011.

[3] Gart, J. J., "An exact test for comparing matched proportions in crossover designs," *Biometrika,* vol. 56, p. 75−80, 1969.

[4] Mainland, D., Elementary Medical Statistics 2nd ed. Saunders, 1963.

[5] Hills, M., and Armitage, P., "The two-period cross-over clinical trial," *British Journal of Clinical Pharmacology,* vol. 8, p. 7−20, 1979.

10 Revision History

This is the original (Version 1.0) Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 1.0 of the study protocol.

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