Short Title:

Biostatistics Safety Analysis Plan – C-09-043

Full Title:

Biostatistics Safety Analysis Plan – C-09-043

Protocol Title:	Long Term Safety Protocol for AcrySof® CACHET® Phakic Lens
Project Number:	25-5223/ NCT01497067
Reference Number:	PC2174.00
Protocol TDOC Number:	TDOC-0010249
Author:	[redacted]
Approvals:	See last page for electronic approvals.

Job Notes:

[redacted]

C-09-043 is the extended safety follow-up study for subjects previously implanted with the AcrySof® CACHET® Phakic Lens (L-series) in clinical studies C-02-23, C-02-40, C-03-21 and C-05-57.

Summary:

Evaluability

All subjects enrolled in the study will be considered evaluable for the safety analysis.

Analysis

The primary objective is to estimate the annualized endothelial cell loss rate (for up to 10 years following date of implantation) of subjects previously implanted with the AcrySof® CACHET® Phakic Lens (L-Series) from clinical studies C-02-23, C-02-40, C-03-21 and C-05-57.

The secondary objective is to collect additional safety data that may identify risk factors for eyes with significant endothelial cell loss.

Safety Variables and Assessments

The safety parameters include:

- Central Endothelial Cell Density
- Adverse Events

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1. STUDY SUMMARY

Study Phase:		Not applicable – Study is observational only
Test Article(s) / Product(s):		AcrySof® CACHET® Phakic Lens (L-Series)
Study Dosage / Usage:		Intraocular lenses are implantable medical devices and are intended for long term use over the lifetime of the subject. The phakic intraocular lens may be removed as needed (*e.g.* cataract extraction).
Route of Administration:		Not applicable
Objective(s):		The primary objective is to estimate the annualized endothelial cell loss rate (for up to 10 years following date of implantation) of subjects previously implanted with the AcrySof® CACHET® Phakic Lens (L-Series) from clinical studies C-02-23, C-02-40, C-03-21 and C-05-57. The secondary objective is to collect additional safety data that may identify risk factors for eyes with significant endothelial cell loss.
Study Population:		Subjects previously implanted with the AcrySof® CACHET® Phakic Lens (L-series) in clinical studies C-02-23, C-02-40, C-03-21 and C-05-57 (includes subjects who have had the lens explanted for any reason).
Structure:	☐ Parallel Group	Duration of Treatment: Duration of Assessment:
	☐ Crossover	Number of Treatments: Number of Sequences: Number of Periods: Duration of Periods: Washout Between Periods: ☐ Yes ☐ No
	☒ Other	No control, open label study Duration of Treatment: Subjects to be followed for 5 to 7 years (10 years from the time of implantation).
Multi-center:	☒ Yes ☐ No	Number of Centers: Up to 35

Masking:	X	None
		Observer-Masked
		Patient-Masked
		Double-Masked

Randomization:		Yes Group Assignment Ratio:
	X	No

Concurrent Control:	X	None	
		No Treatment	
		Placebo	
		Active	Specify:
		Other	Specify:

Estimated Total Sample Size: Required: N/A
Planned: Up to 1321 eyes

Safety Variable(s): Primary Safety

- Central endothelial cell density
- Adverse Events

[redacted]

Adverse Events:	X	Both volunteered and elicited
		Other:

2. SAFETY VARIABLES

2.1. Description

The safety of the AcrySof® CACHET® Phakic Lens (L-Series) will be assessed for the following safety parameters:

- Central Endothelial Cell Density
- Adverse Events

[redacted]

[redacted]

2.2. Measurement Time

Table 2.2.-1: Study Plan

	Nominal Time ± Visit Window Limits												
Procedure / Assessment	Entrance Visit [a]	Year 4/4A[c] Day[b] 1429 – 1550	Year 5/5A Day 1794 – 1915	Year 5.5/5.5A Day 1976 – 2097	Year 6/6A Day 2159 – 2280	Year 6.5/6.5A Day 2341 – 2462	Year 7/7A Day 2524 – 2645	Year 7.5/7.5A Day 2706 – 2827	Year 8/8A Day 2889 – 3010	Year 8.5/8.5A Day 3071 – 3192	Year 9/9A Day 3254 – 3375	Year 9.5/9.5A Day 3436 – 3557	Year 10/10A Day 3619 – 3740
Central [redacted] ECD		X	X	X	X	X	X	X	X	X	X	X	X
[redacted]													
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X
[redacted]													

[a] The subject's initial C-09-043 study examination may be Form 9 or later (*i.e.*, Form 9, 10, 11, etc.). Point of entry is determined by each subject's eye surgery date and the next available visit listed here to enable continued yearly examination. As in previous studies, subjects with the AcrySof® CACHET® Phakic Lens (L-Series) implanted in both eyes will have separate study visits, as needed, for each eye to capture the data within the window of the annual implant date anniversary.

[b] Study Day is relative to the surgery date for each implanted eye.

[c] Data from subject's 2nd implant surgery will be captured on Forms designated with an "A".

2.3. Unit of Analysis

The eye will be the unit of analysis for all safety parameters except for non-ocular adverse events where the unit of analysis will be subject.

2.4. Descriptive Statistics

Descriptive statistics for both eyes combined will be provided for endothelial cell density and adverse events. The statistics presented for continuous variables will include mean, median, standard deviation, number of eyes, minimum and maximum. The statistics for categorical variables will include sample size and percentage in the categories.

3. DATA SETS ANALYZED

3.1. Safety

3.1.1. EVALUABILITY STRATEGY

All subjects enrolled in the study will be considered evaluable for the safety analysis. All data collected in the study will be considered evaluable for the safety analysis with one exception. For subjects who have their AcrySof® CACHET® L-series Phakic Lens explanted and not replaced with another AcrySof® CACHET® L-series Phakic Lens, the post-explantation endothelial cell density data will be excluded from the statistical analyses other than a post-explant endothelial cell loss analysis. The post-explantation data will be used in subject narratives. The final evaluability (exclusion of post-explantation endothelial cell density data) will be determined prior to database lock.

3.1.2. HANDLING OF DROPOUTS OR MISSING DATA

All data will be used in the analyses. No imputation will be carried out for missing data.

4. ANALYSIS OF SAFETY

4.1. Maintenance of Endothelial Cell Density

4.1.1. DESCRIPTION

Endothelial cell density will be collected [redacted] centrally [redacted]. Three images at the center of the cornea [redacted] are planned. Data reported on the CRF by the central reading center will include endothelial cell density and number of cells that were analyzed for each analyzable image. All recorded data from images will be used in the analysis. Although the central reading center will record the data separately for each image, the average cell density of the analyzable images for an individual eye for each corneal location (central [redacted]) will be used in all summary analyses.

4.1.2. ENDOTHELIAL CELL LOSS OVER TIME (CHRONIC)

Chronic endothelial cell loss is defined as loss from the Day 147-182 (Form 5 or 5A) visit (in the previous studies) to any subsequent visit.

4.1.2.1. CHRONIC CHANGE FROM DAY 147-182 (MONTH 6 IN PREVIOUS STUDIES)

Descriptive statistics will be provided for each scheduled visit, for [redacted] central [redacted] endothelial cell density, for all eyes combined. The statistics presented for endothelial cell density (using the average from the analyzable images for each eye) will include mean, median, standard deviation, sample size, minimum, and maximum.

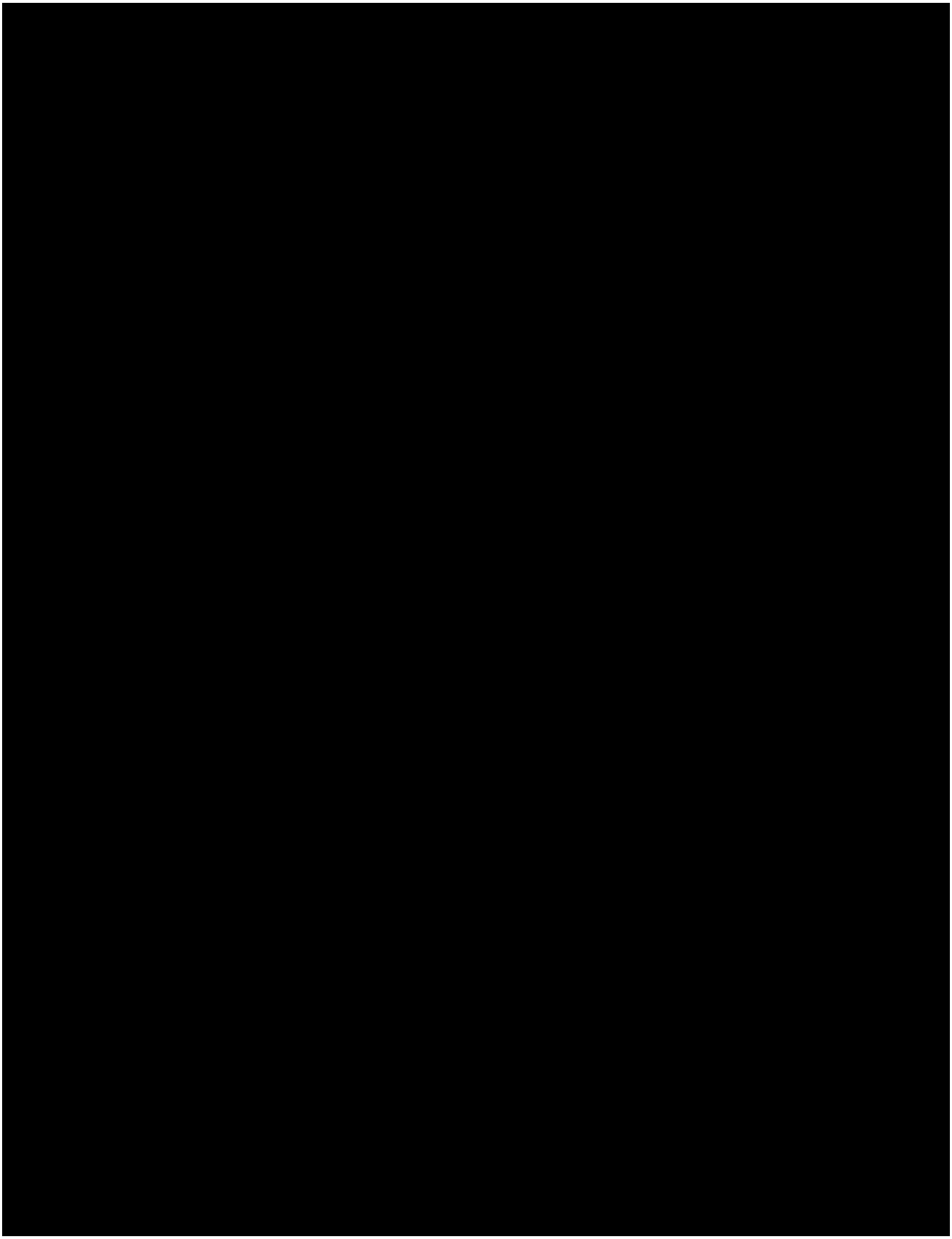
The percent change of mean endothelial cell density over time from Day 147-182 (Form 5 or 5A) in the previous studies to each visit in the current study will be calculated. The actual and annualized percent change of mean endothelial cell density from the Day 147-182 (Form 5 or 5A) exam to each scheduled visit in this study will be calculated and presented along with median, standard deviation, sample size, minimum and maximum. Tables presenting the mean, median, standard deviation, sample size, minimum and maximum of baseline (Form 5 or 5A in previous studies) endothelial cell density and cell density change from baseline to each scheduled visit in this study will be presented for all eyes combined.

4.1.2.2. POSTOPERATIVE CHANGE FROM PREOPERATIVE BASELINE

Descriptive statistics will be provided for change from preoperative baseline (in previous studies) to each scheduled visit in this study, for [redacted] central [redacted] endothelial cell density, for all eyes combined. The statistics presented will include mean, median, standard deviation, sample size, minimum and maximum. The percent change of mean endothelial cell density from preoperative baseline (Form 0 or 0A in previous study) to each scheduled postoperative visit (both in previous studies and this study) will be calculated to determine subjects who had ≥30% loss. A table showing the number and percent of eyes which had the onset of ≥30% endothelial cell loss (central [redacted]) from the preoperative level or central [redacted] of ≤1500 endothelial cells/mm^2 (occurring 6 months or later following implantation) will be presented.

In addition, the mean actual and annualized percent change of endothelial cell density (using the average from the analyzable images for each eye) of all subjects from baseline to each visit will be calculated and presented along with median, standard deviation, sample size, minimum and maximum. These tables will be presented for all eyes combined.

[redacted]



[redacted]

[redacted]

[redacted]

4.2. Adverse Events

4.2.1. ADVERSE EVENT DEFINITIONS

Adverse events (AE), serious adverse events (SAE), adverse device effects (ADE), [redacted] are defined as set forth in Section 12.1. of the protocol.

4.2.2. ADVERSE EVENT ANALYSIS

Adverse events will be coded with MedDRA Preferred Term codes. Descriptive statistics (number and percent of eyes) will be presented for each MedDRA Preferred Term category of ocular adverse events and serious ocular adverse events reported, separately for first

implanted eye, second implanted eye and both eyes combined. Separate tables will be generated for AEs, SAEs, and ADEs. Descriptive statistics (number and percent of subjects) will be presented for each MedDRA Preferred Term category and System Organ Class of non-ocular adverse events and serious non-ocular adverse events reported. In addition, a one-sided upper 95% confidence interval on the percent of each MedDRA Preferred Term code will be calculated [redacted]

[redacted]

[redacted]

A listing of all adverse events and serious adverse events including investigator, subject number, onset day, eye, lens model, causality assessment, severity, outcome and the MedDRA Preferred Term code for the adverse event will also be provided.

5. References

[1]Zarr, JH. Biostatistical Analysis. 3rd ed. Upper Saddle River, New Jersey: Prentice-Hall, Inc;1996: 525-526.

[2]SAS Help and Documentation (SAS Version 9.4). The FREQ Procedure-Binomial Proportion-Wald Confidence Limits.

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
01/30/2018 21:15:21	[redacted]t	Statistician
01/30/2018 21:57:06	[redacted]	Biostatistics
01/31/2018 15:47:28	[redacted]	Medical Safety
02/02/2018 21:59:43	[redacted]	Clinical Lead