Short Title

Long Term Safety Protocol for AcrySof® CACHET® Phakic Lens

Long Title

Long Term Safety Follow-up for Subjects Previously Implanted with the AcrySof® CACHET® Phakic Lens in Clinical Studies C-02-23, C-02-40, C-03-21 and C-05-57

1. TITLE PAGE

Protocol Number:	C-09-043/ NCT01497067
Medical Specialty:	Surgical IOL
Project Name /Number:	Angle-Supported Phakic Refractive IOL / 25-5223
Sponsor Name & Address:	Alcon Research, Ltd. 6201 South Freeway Fort Worth, Texas 76134-2099
Test Article(s) / Product(s):	AcrySof® CACHET® Phakic Lens Models L12500, L13000, L13500 and L14000

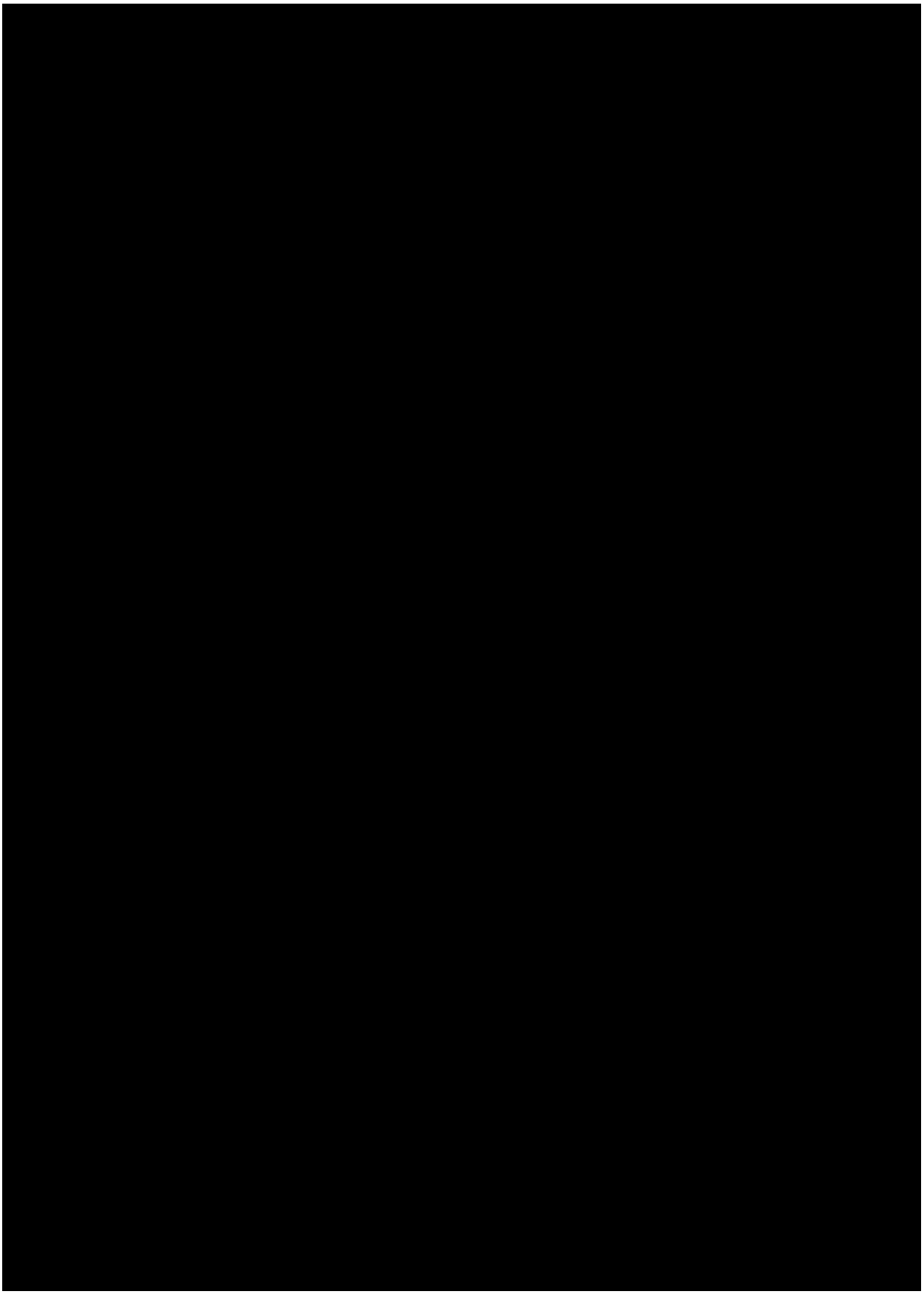
Clinical Investigator:

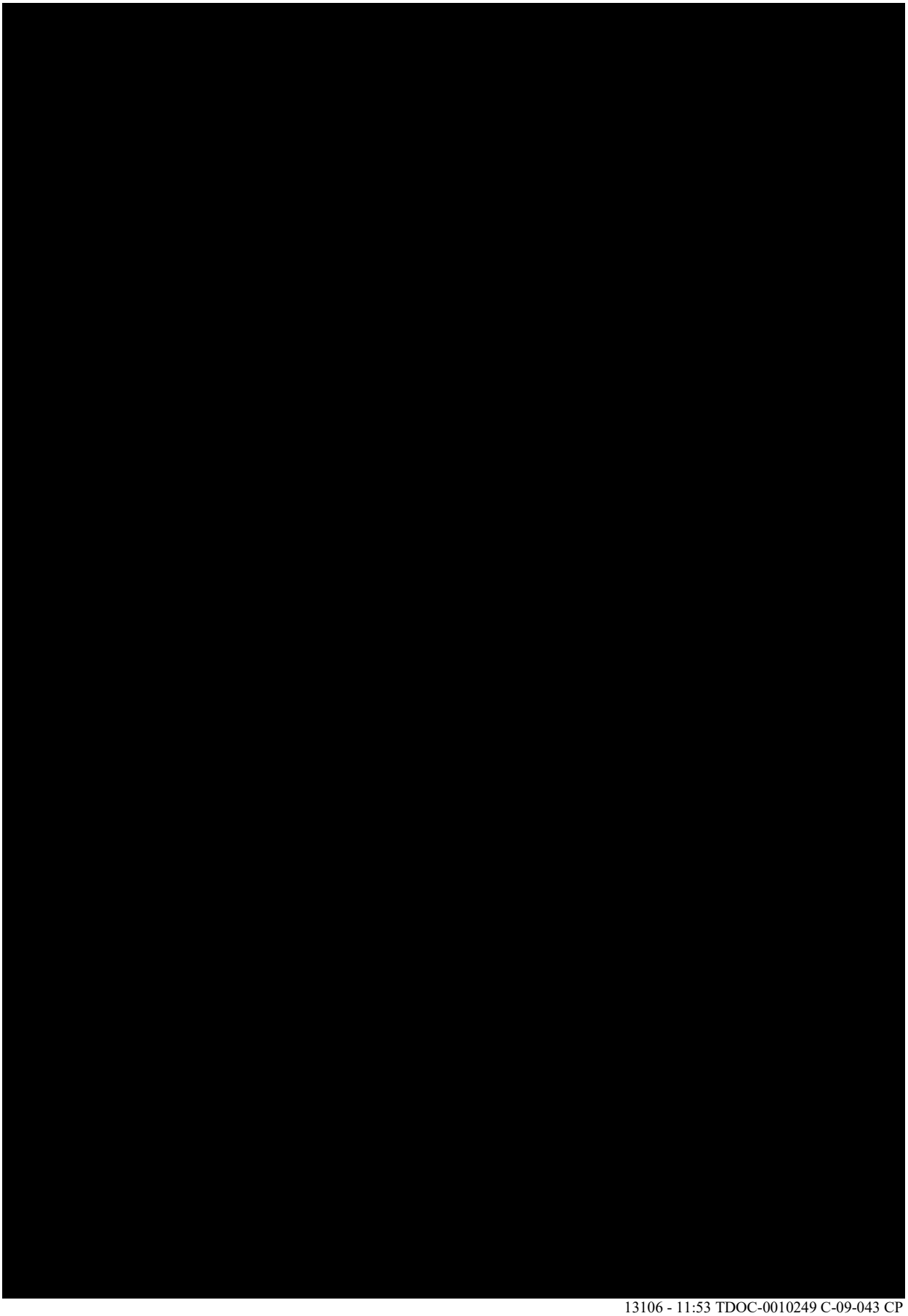
Signature Date

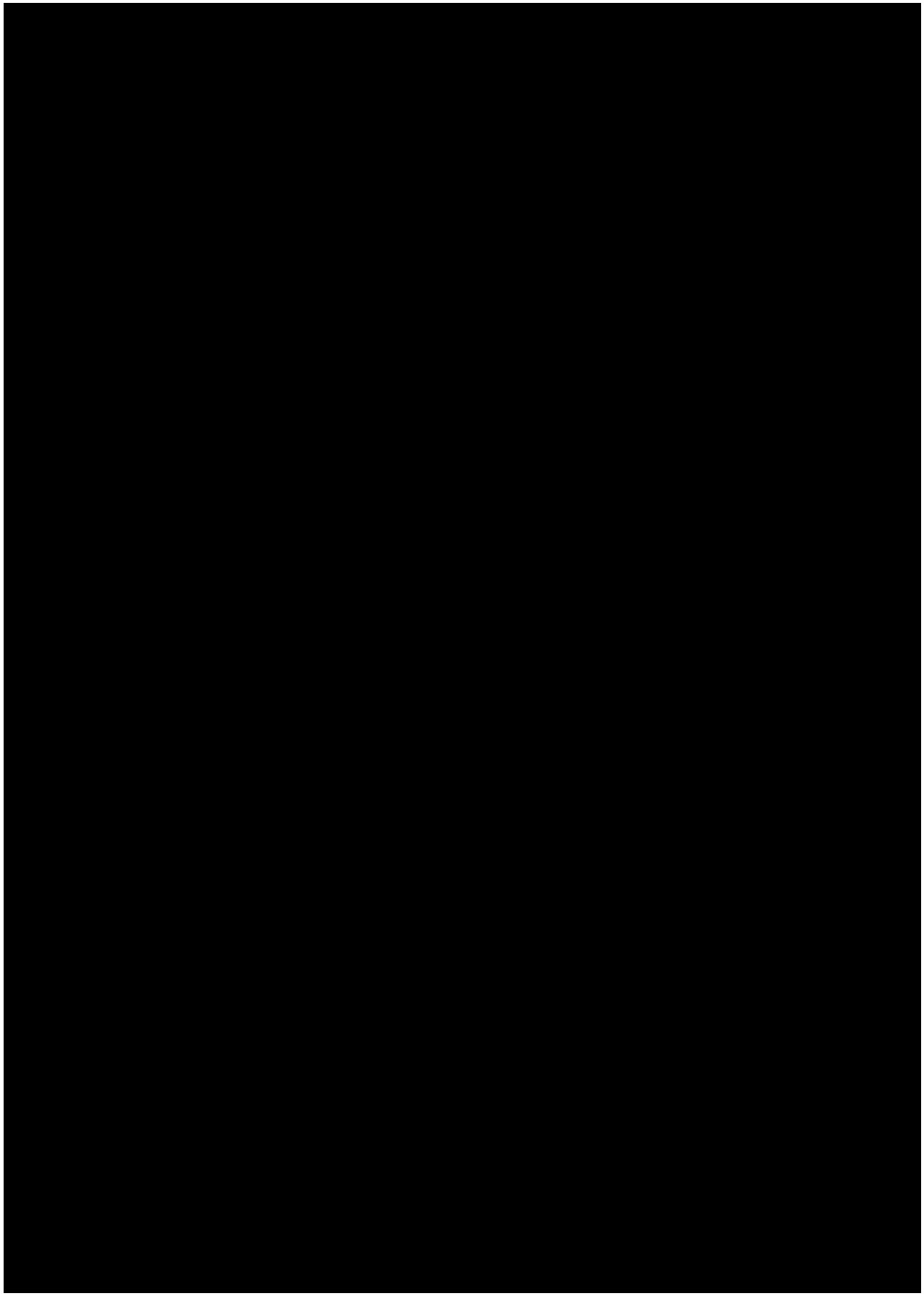
Name & Inv. #
Address
Telephone
As listed on the Statement of Investigator

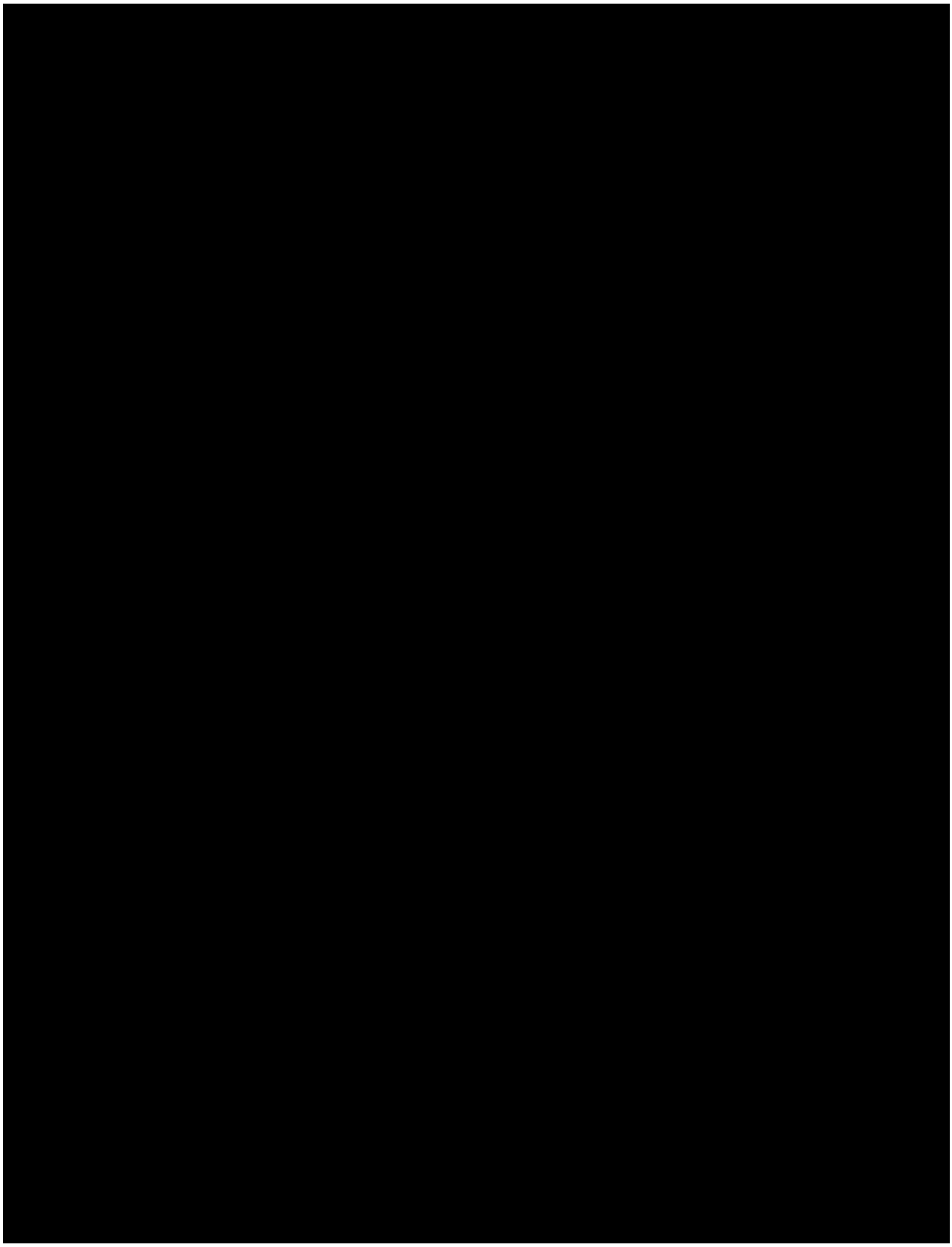
In signing you agree that you have read, understand and will adhere to this protocol.

See last page for electronic approvals.









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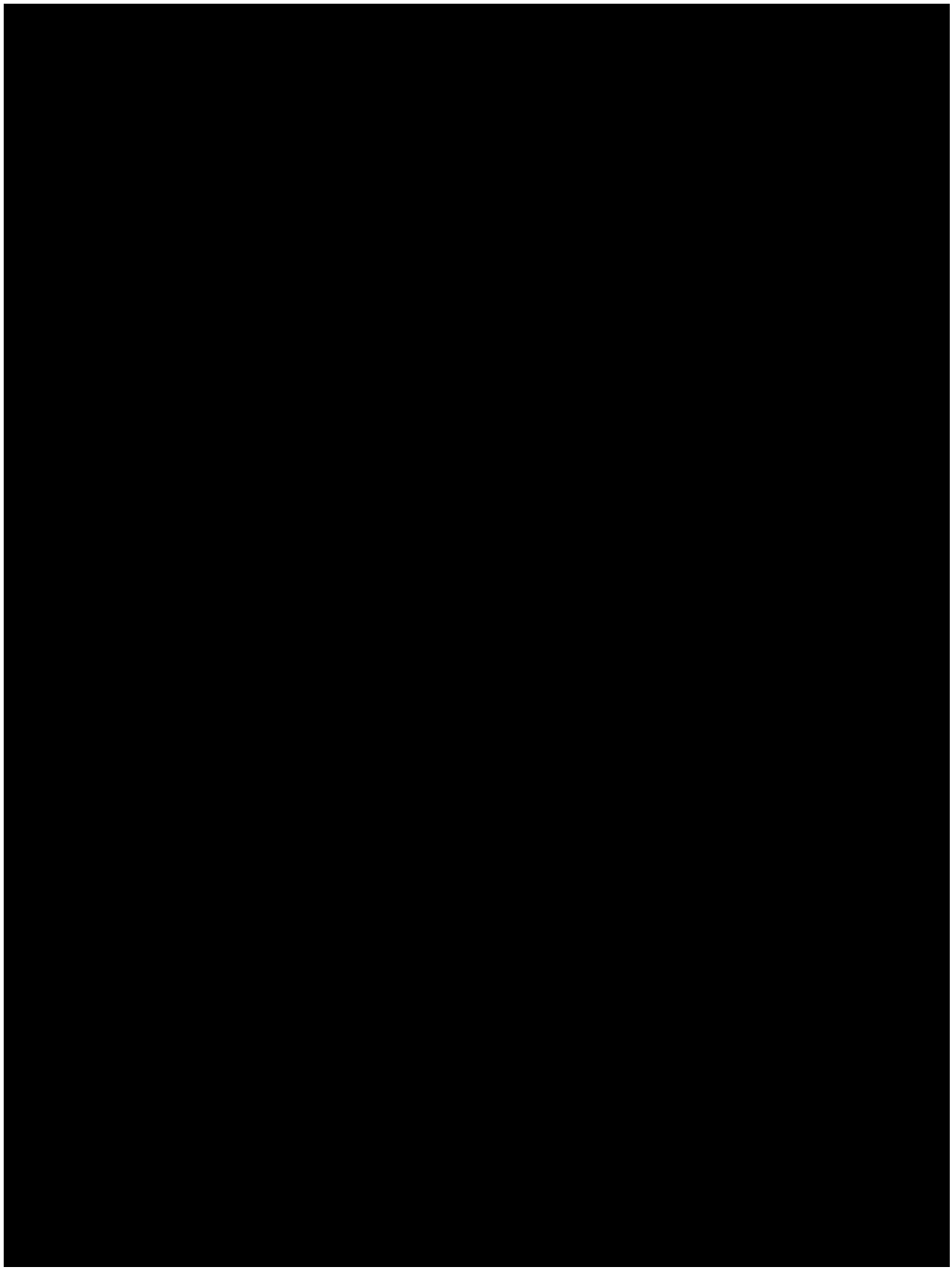

2. SUMMARY

Study Phase:	Not applicable
Financial Disclosure Information for U.S. FDA Submission to be Obtained?	[X] Yes [ ] No
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).
Active Ingredients:	Not applicable
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) during 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
	[X] 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: [X] Yes [ ] No Number of Centers: Up to 35

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

Randomization: [ ] Yes [X] No Group Assignment Ratio:

Concurrent Control:
- [X] None
- [ ] No Treatment
- [ ] Placebo
- [ ] Active Specify:
- [ ] Other Specify:

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

Statistical Rationale Provided: [ ] Yes See Section 11 [X] No

Variable(s):

Primary Efficacy
- None

Secondary Efficacy
- None

[redacted]

Primary Safety
- Central endothelial cell density
- Adverse events

[redacted]

Adverse Events:	X	Both volunteered and elicited
		Other:

Analyses: 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.

Combining data from this study with the data from the subjects' previous studies, the rate of endothelial cell density loss between consecutive visits will be calculated via a paired analysis and descriptive statistics on those rates will be presented. [redacted] Also, the percentage endothelial cell density decrease for each eye from baseline (6 month visit in previous study) to each visit will be calculated via a paired analysis and descriptive statistics for the actual and annualized loss rates will be presented.

[redacted]

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

Descriptive statistics will be provided for central [redacted] endothelial cell densities, [redacted]

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4. INTRODUCTION

Angle-supported Phakic intraocular lenses (IOLs) have been shown to be effective in the correction of myopia and have several benefits over refractive surgery, including reversibility. These IOLs, however, have been associated with complications including possible loss of corneal endothelial cells, pupil ovalization, pigment dispersion, inflammation, synechiae, cataractogenesis, and pupillary block (Kohnen 2010). Of particular concern is possible endothelial cell loss (ECL) which may lead to corneal decompensation. Several factors may lead to ECL, one is possible compression forces against anterior chamber structures. In this study, endothelial cell density [redacted] will be monitored to assess possible causes of ECL.

The ACRYSOF CACHET Phakic IOL is an angle-supported, single-piece, foldable, soft acrylic lens with a chemically bonded UV chromophore and a 6.0 mm meniscus optic. This lens is designed for placement in the anterior chamber to correct moderate to high myopia and provide subjects with a form of vision correction, comfort, and convenience not attainable with spectacles or contact lenses. Because the ACRYSOF CACHET Phakic Lens is foldable, it can be inserted through a small incision, thus reducing the likelihood of induced astigmatism. The mechanical properties of the ACRYSOF material, together with the design of the ACRYSOF CACHET Phakic Lens, should result in lower forces against the anterior chamber angle.

Phased clinical studies have been completed, or are ongoing, to assess the safety and effectiveness of the ACRYSOF CACHET Phakic IOL. Models SA3M25, SA3M13, and SA3M35 (the SA-series) were studied as part of European (EU) clinical investigations conducted under Protocol C-99-38 (EU Phase 1) and Protocol C-01-22 (EU Phase 2). Models RA6M13 and RA6M35 (the RA-series) were studied as part of the U.S. clinical investigation conducted under Protocol C-02-23 (U.S. Phase 1). Models L12500, L13000, L13500, and L14000 (the L-series) are being studied (two studies are complete) in four protocols: as part of an EU clinical investigation conducted under Protocol C-02-40 (EU Phase 3); a completed U.S. clinical investigation conducted under Protocol C-02-23 (U.S. Phase 1 (second eyes only) and Phase 2); a completed U.S. clinical investigation conducted under Protocol C-05-57 (U.S. Phase 3); and also as part of a Canadian clinical investigation conducted under Protocol

C-03-21 (Canada Phase 3). Interim data from these ongoing clinical trials were reported in Kohnen 2009 and Knorz 2011.

Based on the results available to date, the overall risks for subjects implanted with the ACRYSOF CACHET Phakic IOL are representative of known risks associated with intraocular surgery and the implantation of a phakic IOL. Continued monitoring of postoperative corneal health, including endothelial cell density and cell morphology, is recommended to ensure safety of the subject. Endothelial cell loss will be followed in this study to understand the long-term safety of the ACRYSOF CACHET Phakic IOL (L-series). Only L-series IOLs will be followed in this study since this is the model that will be submitted for market approval. The ACRYSOF CACHET Phakic IOL is marketed outside the United States.

A summary of clinically significant findings from non-clinical and clinical studies and a summary of known and potential risks and benefits to human subjects can be found in the Clinical Investigator's Brochure (CIB-0021; TDOC-0006479) for the ACRYSOF CACHET Phakic IOL family including the following models: Models SA3M25, SA3M13, and SA3M35 (the "SA" series, all with a 5.5 mm diameter optic size), Models L12500, RA6M13 / L13000, RA6M35 / L13500, and RA6M14 / L14000 (the "RA" series and "L" series all have a 6.0 mm diameter optic size).

5. OBJECTIVE(S)

The primary objective is to estimate the annualized endothelial cell loss (ECL) rate (for up to 10 years following date of implantation) of subjects previously implanted with the ACRYSOF CACHET Phakic Lens (L-series) within 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 ECL.

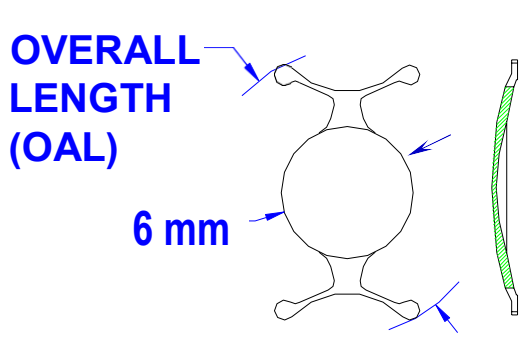
6. TEST ARTICLE(S)

6.1. Identification

Lenses will not be supplied during this clinical trial, as subjects invited to enroll will have been 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 ACRYSOF CACHET Phakic Lens is an angle-supported, anterior chamber, single piece lens composed of a cross-linked soft acrylic polymeric material with a chemically bonded UV-absorber. This is the same acrylic material that is currently used in the optic of the globally marketed ACRYSOF multi- and single-piece IOL Models MA30BA, MA60BM, SA30AL, and SA60AT.

The ACRYSOF CACHET Phakic Lens models have a 6.0 mm diameter meniscus optic and are intended for implantation in the anterior chamber angle. The overall lengths of these models vary from 12.5 mm to 14.0 mm as follows: Models L12500 (12.5 mm), L13000 (13.0 mm), L13500 (13.5 mm) and L14000 (14.0 mm). The dioptric range of these IOLs is -6 to -16.5D.



OAL (mm)	Model
12.5	L12500
13.0	L13000
13.5	L13500
14.0	L14000

6.2. Usage

The ACRYSOF CACHET Phakic Lens is a permanent implantable medical device, thus the expected duration of individual subject use, and exposure, is expected to be for the remainder of the subject's life, or until cataract extraction is needed.

6.3. Test Article Accountability Procedures

Damaged test articles or explanted lenses must be packaged in a biohazard bag and returned to the sponsor at the following address:

Attn: [redacted]
Mail Code: [redacted]
Alcon Research, Ltd.
6201 South Freeway,
Fort Worth, TX 76134

[redacted]

In cases of explanted lenses, all information related to the adverse device effect or serious adverse event should be entered into the EDC system on the *Adverse Device Effect and Serious Adverse Event Form* within 24 hours of the investigator's or site's awareness of the event. Please include a printed copy of the completed *Adverse Device Effect and Serious Adverse Event Form* with product returns.

Refer to Section 12 for additional information on reporting any [redacted], adverse device effects, or serious adverse events.

7. SUBJECTS

7.1. Subject Population

Subjects previously implanted (unilaterally or bilaterally) 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). Up to 778 subjects will be enrolled; up to 65 subjects per site. No vulnerable population is planned.

7.2. Inclusion Criteria

1. Subjects previously implanted (including subjects who have had the lens explanted for any reason) with an ACRYSOF CACHET Phakic Lens (L-Series) from clinical studies C-02-23, C-02-40, C-03-21 and C-05-57 and are eligible for continued follow-up (ie, exited from their previous study).
2. Subjects are willing and able to complete the yearly postoperative study visits.
3. Subjects are able to understand and sign a statement of informed consent.

7.3. Exclusion Criteria

None

8. STUDY DESIGN

8.1. Study Design

Subjects enrolled in this study will attend postoperative visits for up to 10 years following the date of implantation and will be able to enroll at any time for the duration of this trial. These subjects will be followed postoperatively to Year 10/10A (3619 – 3740 days) at appropriate intervals as defined in Section 9.1.

[redacted]

8.1.1. IMPLANT REMOVALS

During this clinical investigation, the implant may be removed at any time at the request of the study subject and/or if the investigator believes it appropriate (eg, cataract surgery). An implant removal is considered a Secondary Surgical Intervention and requires the completion of a Serious Adverse Event Form (see Section 12). Test article will not be provided for IOL replacement. Subjects with implant removals will not be exited from the study.

8.2. Methods Used to Minimize Bias

Randomization and masking are not used in this study. However, all investigators and study coordinators will receive common training (including specular image collection and angle measurements) to ensure consistent application of the methods specified in the protocol. Also, the same inclusion criteria are to be applied by all investigators and all patients meeting inclusion criteria will be invited to participate in the study. Furthermore, explanted subjects will not be discontinued. Bias will also be minimized by using a central reading center for corneal endothelial cell analysis. In addition, study duration will be sufficient to examine the effect of the lens on endothelial cells (ie, density [redacted]).

8.3. Clinical Study Termination

An investigational site can be suspended or terminated by the Sponsor if monitoring or auditing identifies serious or repeated deviations. While possible, it is not anticipated that the entire study will be terminated. If the study or an investigational site is terminated, the investigator and any regulatory authorities will be informed with 5 days of the decision. Investigators would be given instructions for the procedures to be followed to assure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IEC/IRB's of the early termination of the trial or of the investigational site.

8.4. Regulatory Documentation and Records Retention

Essential documents must be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the latest marketing approval). The Sponsor will notify the Investigator(s)/institution(s) when the study-related records are no longer required.

8.5. Data Management

A Clinical Data Management System (CDMS) will be used to collect and validate clinical data. The CDMS will conform to the Sponsor's requirements for system setup and data security. Data validation will be performed by electronically generated checks and manual reviews. Final data and related documentation will be retained according to the Sponsor's retention schedule.

8.6. Data Review and Handling

Clinical data captured at the sites will be entered into electronic case report forms (eCRFs) within the CDMS. SAS datasets (SAS Institute Inc. Cary, NC , USA) for the clinical data will be downloaded from the electronic data capture (EDC) database after database lock, or as needed throughout the clinical trial. All SAS datasets will be housed in a secured network area storage and will be accessible to the Sponsor using read only roles. The datasets will reflect the current protocol. The datasets will reflect the current state of the database, all

previous actions and values of the data will be captured in the audit trail within the EDC database.

Any change or correction to data reported on a CRF will be updated and/or explained within the CDMS. The original entry and all actions applied to the CRF after initial entry will be maintained in the audit trail (ie, an audit trail will be maintained that documents the action, user and date of change or explanation).

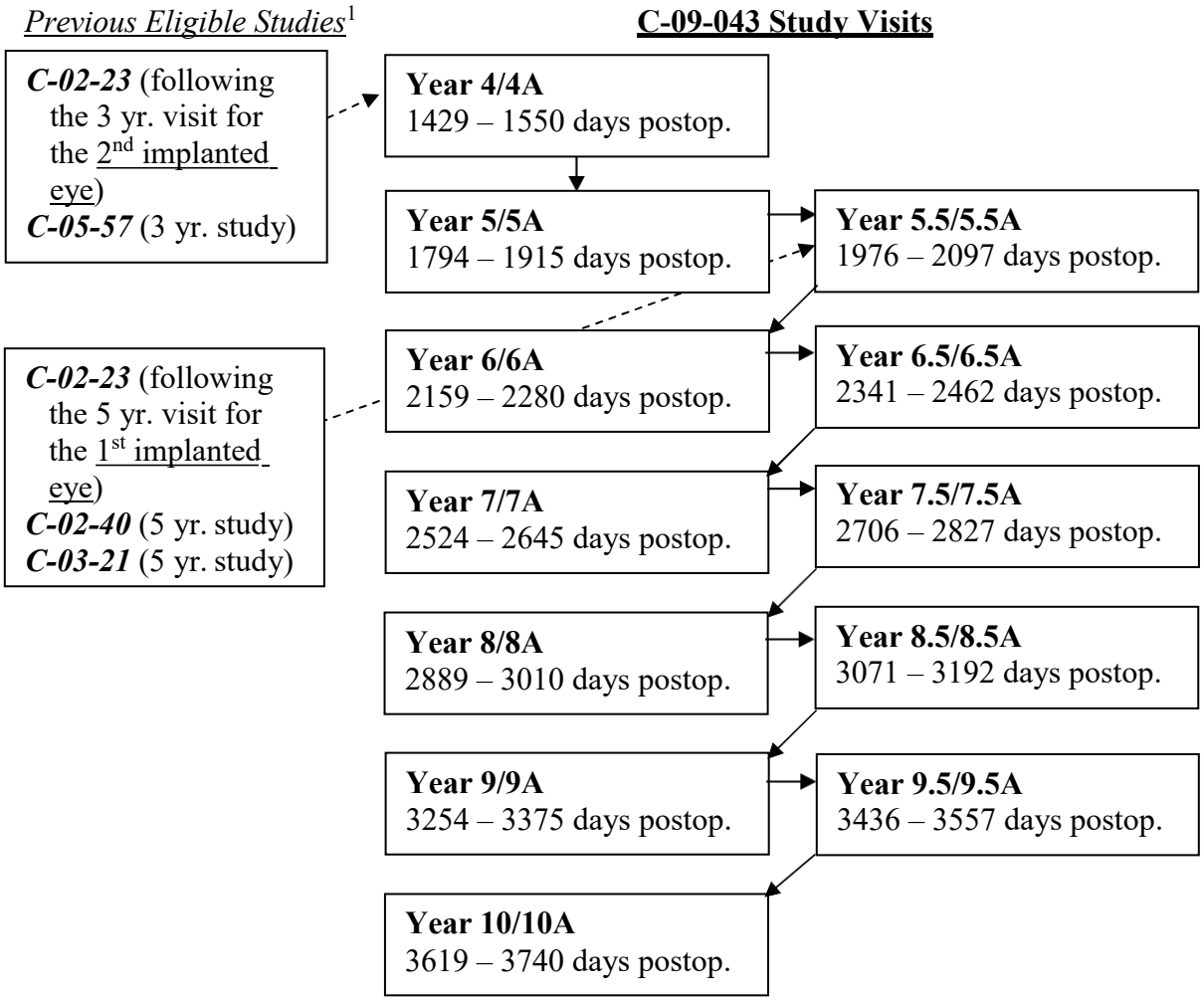
8.7. Data Publication

Results will be published through clinicaltrials.gov.

9. STUDY PROCEDURE

9.1. Study Visits and Examination

An Entrance Visit will be completed upon a subject's enrollment. Subjects may enroll in the study at any time, thus the Entrance Visit may coincide with any visit (Year 4/4A to Year 10/10A).



[1] Only eyes previously implanted with an L-series lens are eligible for enrollment.
[2]"A" designates forms that are completed for a Subject's 2nd implanted eye.
Note: In some cases, more than six months may have passed since a subject completed the previous study. These subjects will be examined at the next appropriate time-point following entrance to the study.

Postoperative visits for the first and second implants may be performed simultaneously if both visits fall within the proper timeframes specified for each eye.

Subjects examined subsequent to Day 3740 and prior to study exit (eg, a planned visit occurring after the last study plan visit) will be included in the Year 10/10A analysis if:

a) no Year 10 or 10A Form was received previously, or
b) the original Year 10 or 10A exam was early, or
c) the subject was previously unavailable for the visit or previously discontinued.

Each required examination must be recorded on the corresponding electronic Case Report Forms (eCRFs) in a timely manner.

9.2. Entrance Visit

The following information will be recorded on the Entrance Visit eCRF:

9.2.1. INFORMED CONSENT

Prior to undergoing study specific measurements, subjects will be asked to give informed consent and sign the Institutional Review Board (IRB) or Institutional Ethics Committee (IEC) approved Informed Consent Document (ICD). Only subjects who have signed the informed consent and qualified to be in the study by meeting all inclusion criteria will be enrolled into the study.

The Investigator, or designee, will explain the clinical trial to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The subject must be provided an opportunity to ask questions of the Investigator, and if required by local regulation, other qualified personnel. The Investigator must provide the subject with a copy of the consent form written in a language the subject understands. The consent document must meet all applicable local laws and will provide subjects with information regarding the purpose,

procedures, requirements, and restrictions of the clinical trial, along with any known risks and potential benefits associated with the investigational product, the available compensation, and the established provisions for maintaining confidentiality of personal, protected health information. Subjects will be told about the voluntary nature of participation in the clinical trial and will be provided with contact information for the appropriate individuals should questions or concerns arise during the clinical trial. The subject also will be told that their records may be accessed by appropriate authorities and Sponsor-designated personnel. The Investigator must keep the original, signed copy of the consent and must provide a duplicate copy to each subject.

9.2.2. INCLUSION CRITERIA

Refer to the list of Inclusion criteria in Section 7.2. to ensure that the subject meets all qualifications for participation (ie, inclusion criteria).

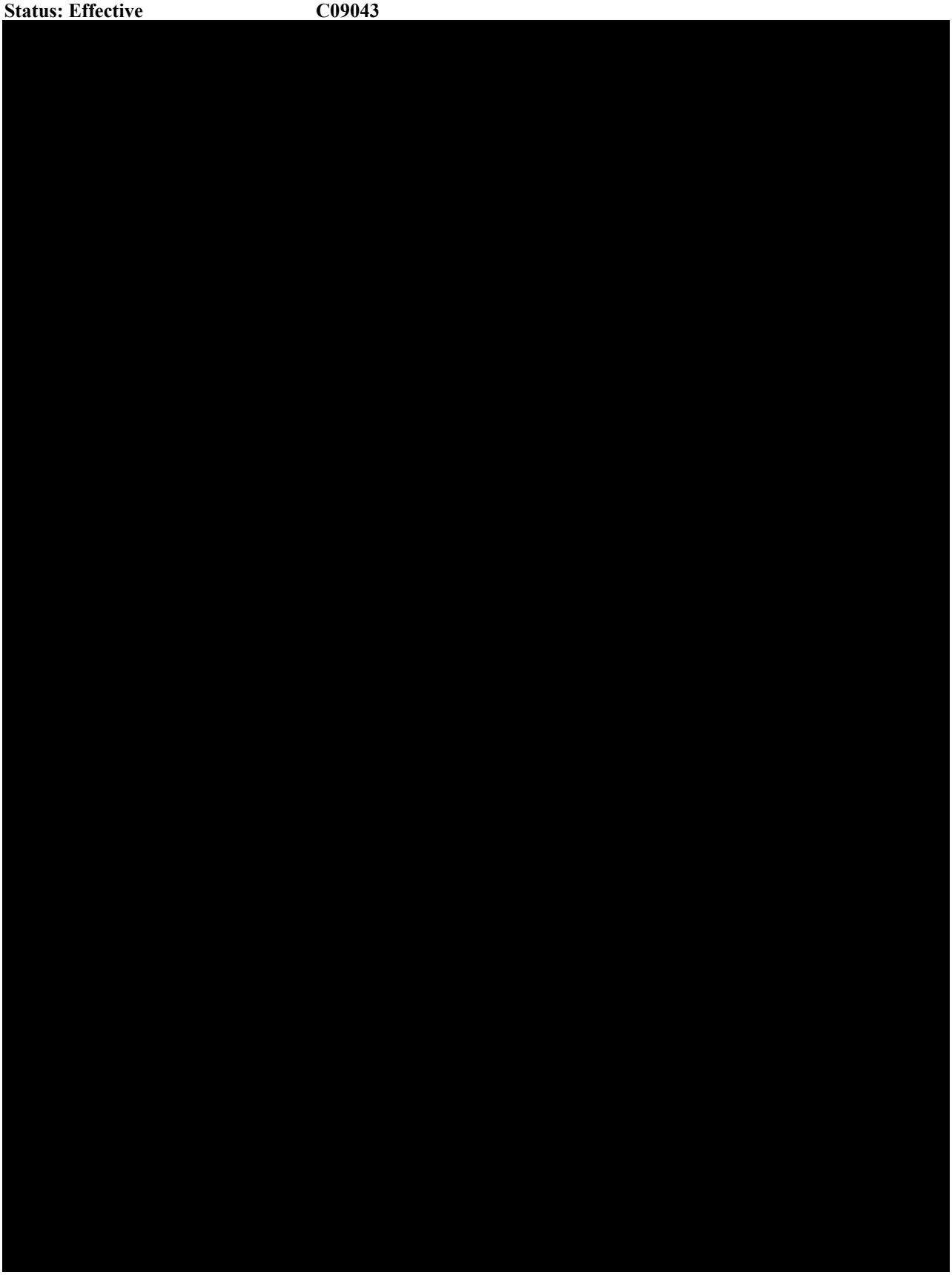
9.2.3. ENROLLMENT INFORMATION

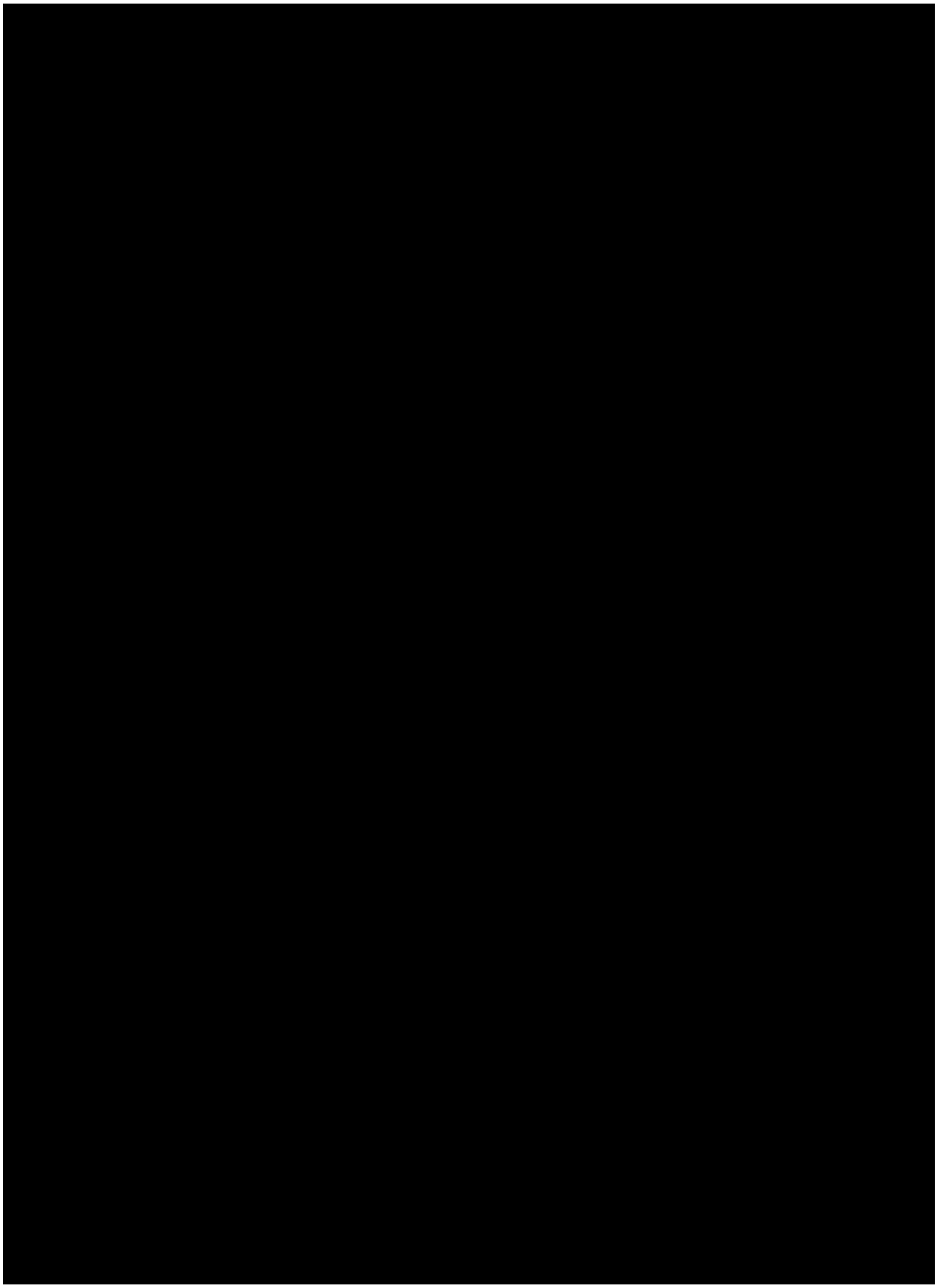
Record the following information from the subject's previous (C-02-23, C-02-40, C-03-21, or C-05-57) study: Protocol number, investigator number, subject number, study eye(s), whether or not the lens was replaced, and the Visit in which the subject entered the C-09-043 study. If the fellow eye has been implanted with any Phakic IOL (at any time), or if the ACRYSOF CACHET Lens has been replaced with another IOL, please record lens information ("other IOL").

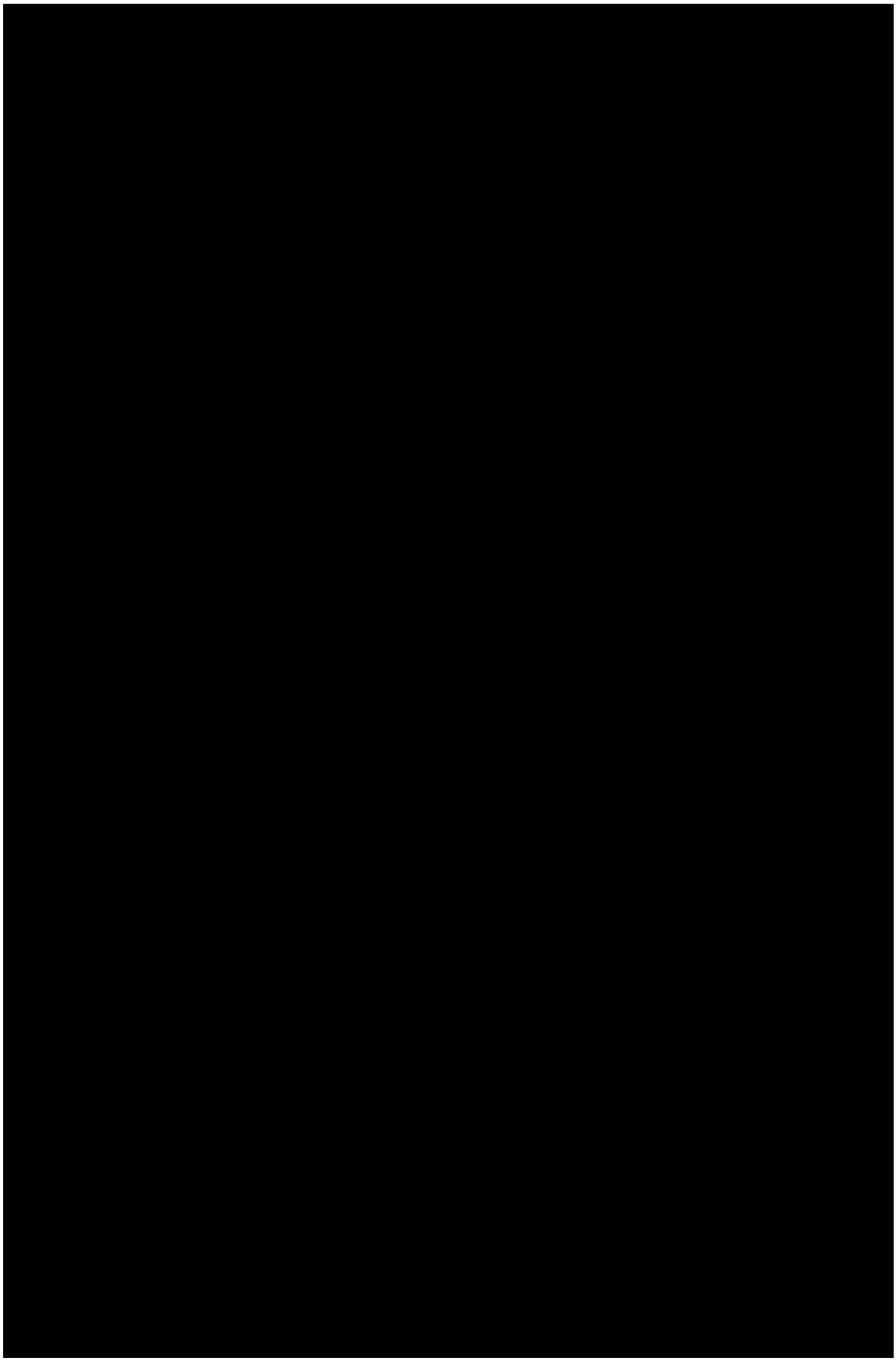
9.2.4. MEDICAL HISTORY

Record all relevant ocular and relevant non-ocular medical history.

[redacted]







[redacted]

9.3.7. ENDOTHELIAL CELL DENSITY ANALYSIS

Endothelial cell density [redacted] will be measured using the same methods as in the previous studies (C-02-23, C-02-40, C-03-21, C-05-57). The Konan Noncon-Robo specular microscope will be used to photograph corneal endothelial cells. Three images at the center of the cornea [redacted] shall be obtained.

[redacted]

Images shall be stored on the computer hard drive at the clinical site. Electronic copies of the images will be sent to a central reading center for analysis. For consistency, the central reading center ([redacted]) used for the previous studies, will be used for this study; Alcon personnel will not be involved in image analysis. The process for analyzing images at [redacted] will remain unaltered from that done in previous studies. Briefly, images received at [redacted] will be reviewed by an initial reader and assessed for image quality. If image quality is acceptable then images will be analyzed. If images are deemed unanalyzable, then images will not be analyzed, and the site and Sponsor will be notified. (If there is a trend of unanalyzable images for a specific site/delegated study

personnel, retraining will be provided.) The subject will be asked to return and repeat the image capture and new images will be analyzed and used in the dataset. Analyzed images will be audited by a quality control reviewer [redacted]

Data reported by the central reading center will include endothelial cell density, [redacted] The site will receive a copy of the analysis to enter results in eCRFs.

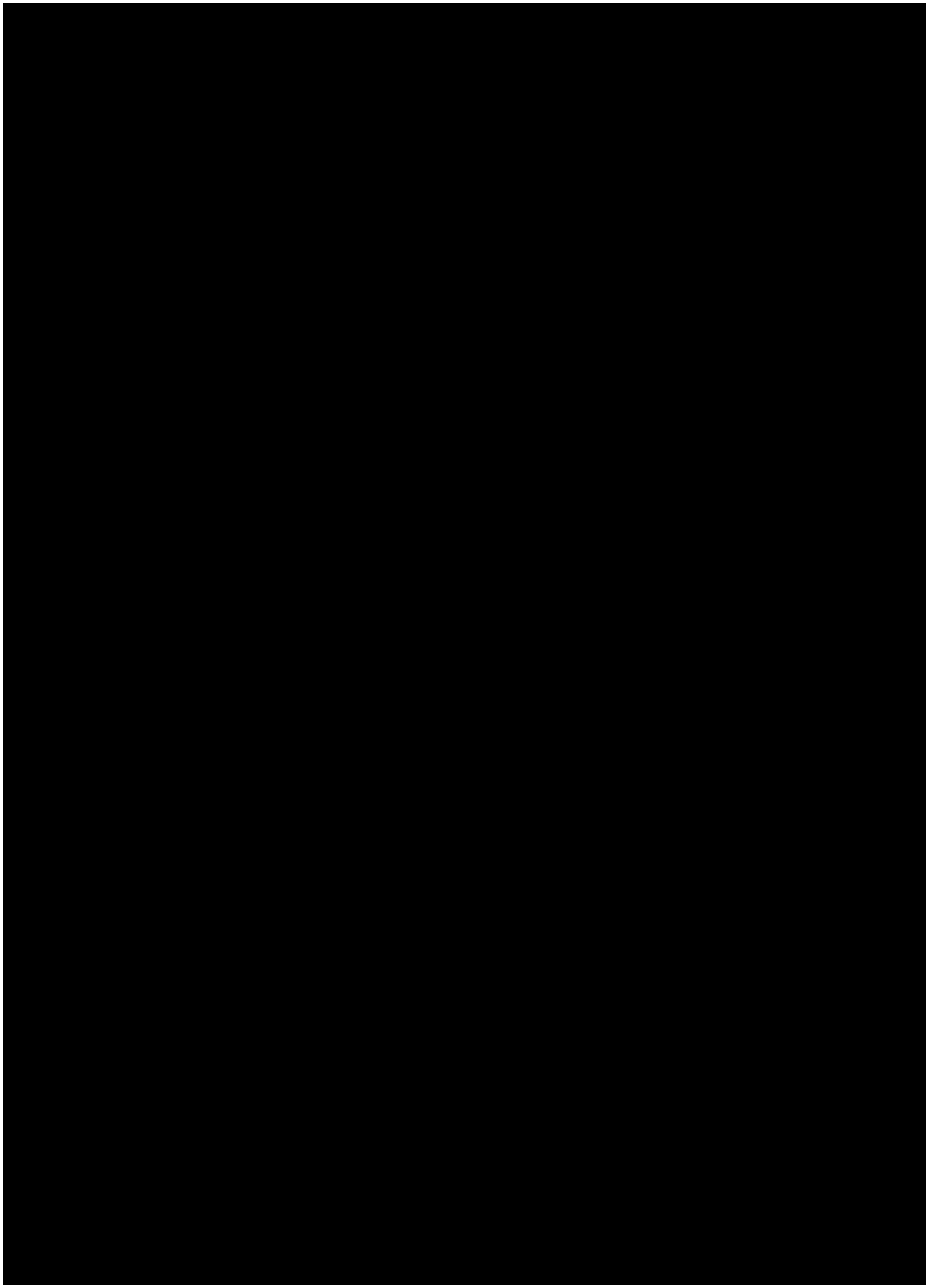
The critical ECD threshold needed to sustain corneal endothelial cell function varies among individuals. Thus, it is critical to have regular examinations of the cornea every 6 months.

Criteria that may warrant more frequent examinations include:

- <1500 cells/mm^2 (central [redacted])
- >10% ECL in one year
- >30% ECL from preoperative baseline

[redacted]

When the central ECD approaches approximately 1500 cells/mm^2, the investigator should consider the potential need to undergo IOL explantation to reduce the risk of corneal decompensation and subsequent surgical interventions (such as corneal transplantation or DSEK). [redacted]



[redacted]

9.4. Unscheduled Visits

If a subject is examined more than once during any of the scheduled follow-up periods or if the subject is examined between scheduled follow-up periods, or if there is an unscheduled planned treatment delaying exit, an Unscheduled Visit Form must be completed.

If, during the visits for the 2nd eye implanted (Year 4A through 10A Forms), a clinically-relevant finding is noted for the 1st eye implanted, an unscheduled visit form must be completed to record the data for the 1st eye implanted; the same is true if a clinically-relevant finding is noted on the 2nd eye during the visits for the 1st eye. If the second eye examination is being conducted at the same time as a scheduled first eye examination (with both examinations occurring during the correct time frame) the findings from each eye should be recorded on the applicable visit form and not on an unscheduled visit form.

9.5. Missed Visit – "Subject Unavailable"

If a subject unavoidably misses a scheduled exam, all reasonable efforts must be made to have the subject rescheduled within the same exam follow-up period. The investigator must show diligence in trying to schedule the subject for all of their postoperative exams. All attempts to contact the subject must be documented in the source documentation and the subject's medical records. If an exam cannot be rescheduled, the corresponding visit pages will be marked "missed visit, subject unavailable". Please do not classify the subject as "unavailable" until rescheduling has been attempted and the time frame for the postoperative exam has expired.

If a subject is unable to return for the final study visit (Year 10 or 10A), complete the Exit Form with the appropriate reason for discontinuation indicated.

9.6. Discontinued Subjects

Discontinued subjects will not be replaced. If a subject is discontinued from the study due to their death, the Exit Form and a Serious Adverse Event/Adverse Device Effect Form must be completed.

Subjects who require an IOL explant will not be discontinued and all reasonable efforts must be made to follow them up through their final study visit (Year 10/10A).

9.7. Subject Lost to Follow-Up

A subject is considered lost to follow-up if:

a) a postoperative Study Visit is overdue, all efforts to contact the subject for an examination have failed, the subject's last visit window has closed, or
b) the subject is unable to make future office visits, or
c) the subject has moved and is no longer able to be examined.

If a subject moves before completing all of the required visits, reasonable efforts must be made for the subject to return to the implanting investigator or to the closest investigational site for follow-up. Reimbursement for reasonable travel costs may be available from the Sponsor and will be addressed on a case-by-case basis.

9.8. Patient Pregnancy

Subjects who become pregnant during the study will not be discontinued.

10. ANALYSIS PLAN

10.1. Subject Evaluability

All subjects enrolled in the study will be considered evaluable for the safety analysis. The final evaluability (exclusion of post-explantation endothelial cell density data) will be determined prior to database lock.

10.2. Analysis Data Sets

10.2.1. SAFETY

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. The post-explantation data will be used in subject narratives and graphs.

10.3. Demographic and Baseline Characteristics

Demographic and baseline information from the subjects' previous study will be summarized using frequency distributions for categorical parameters and descriptive statistics (number, median, minimum, maximum, mean and standard deviation) for continuous parameters.

10.4. Safety Analysis

The safety parameters include:

- Central Endothelial Cell Density
- Adverse Events

[redacted]

[redacted]

The primary objective is to estimate the annualized endothelial cell density 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 density loss.

10.4.1. PRIMARY SAFETY

10.4.1.1. CENTRAL ENDOTHELIAL CELL DENSITY

Descriptive statistics for central endothelial cell density, for each scheduled visit (including data from previous studies), will be provided. Descriptive statistics for central endothelial cell density chronic change (actual and percent) from baseline (6 month visit in previous study) to each scheduled visit will be provided. Descriptive statistics for central endothelial cell density change (actual and percent) between consecutive scheduled visits will be provided. All tables will be generated separately for first implanted eye, second implanted eye, and for both implanted eyes combined. Descriptive statistics include mean, median, standard deviation, sample size, minimum, maximum and confidence limits.

The mean rate of endothelial cell density decrease will be calculated via a paired analysis in order to calculate the mean of the differences between each reporting period.

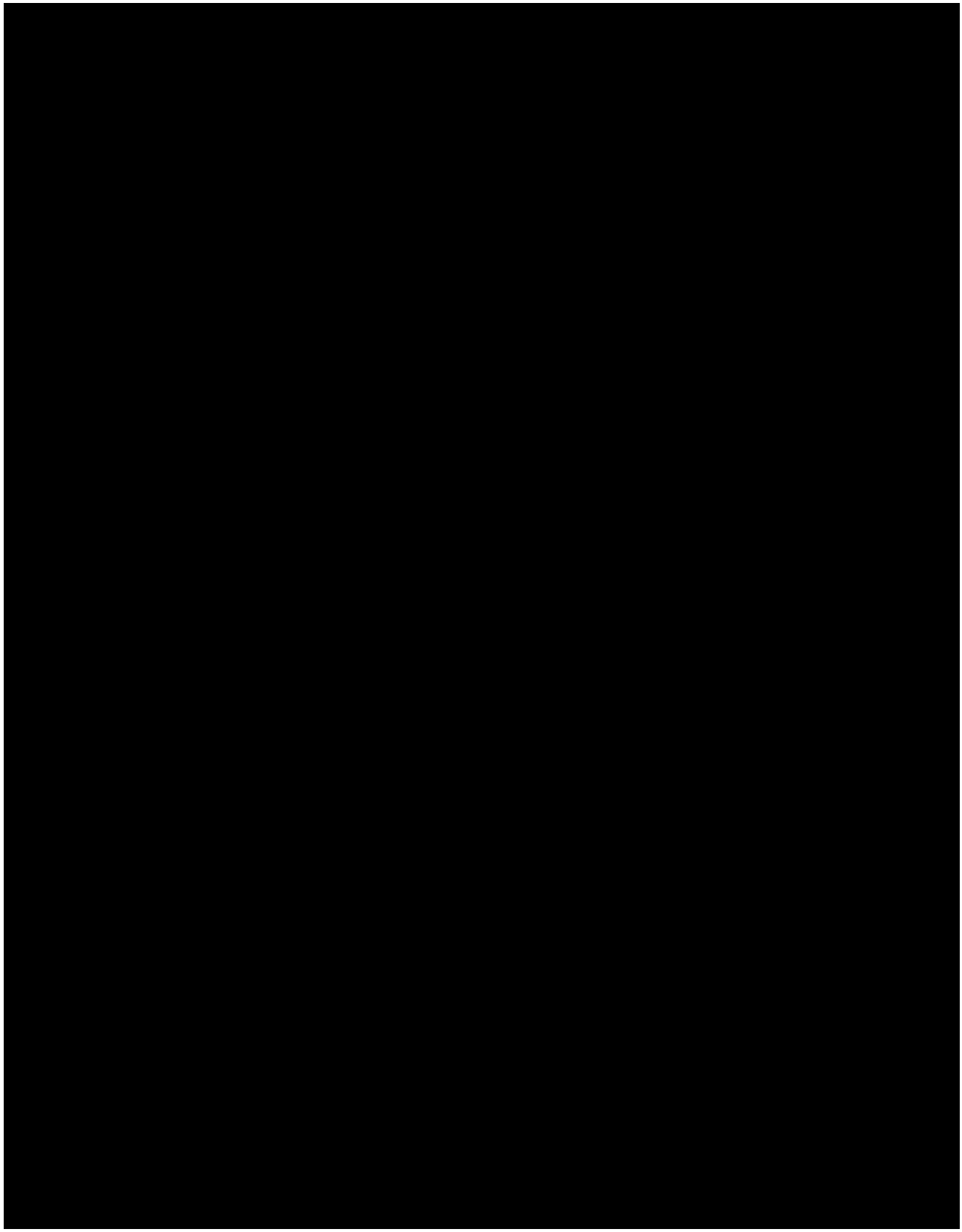
[redacted]

[redacted]

10.4.1.2. ADVERSE EVENTS

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 for both implanted eyes combined. Descriptive statistics (number and percent of subjects) will be presented for each MedDRA Preferred Term category of non-ocular adverse events and serious non-ocular adverse events reported. A listing of all adverse events and serious adverse events reported during the study will also be provided.

[redacted]



[redacted]

[redacted]

10.6. Handling of Missing Data

All evaluable data will be used in the analyses; however, no imputation will be carried out for missing data.

10.7. Multiplicity

No formal hypothesis testing is planned for any parameters and therefore no multiplicity adjustments are needed.

[redacted]

11. SAMPLE SIZE JUSTIFICATION

The sample size will reflect the number of sites and subjects agreeing to participate.

All available and willing subjects meeting inclusion criteria will be included in the study (up to 778 subjects; up to 1321 eyes).

12. [redacted] ADVERSE EVENTS

12.1. General Information

Definitions

[redacted]

Adverse Event (AE) – any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. *Note: For subjects, this definition includes events related to the investigational medical device or the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.*

See Figure 12.1.-1 for categorization of adverse events.

Adverse Device Effect (ADE) – adverse event related to the use of an investigational medical device. *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 investigational medical device.*

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

Serious Adverse Event (SAE) - adverse event that led to any of the following:

- Death.
- A serious deterioration in health 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, or a procedure required by the clinical investigation plan, 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 medical or surgical intervention to prevent a) or b), or any ocular secondary intervention.

e) any indirect harm as a consequence of incorrect diagnostic test results when used within manufacturer's instructions for use.

- Fetal distress, fetal death, or a congenital abnormality or birth defect.

See Figure 12.1.-2 for categorization of SAEs.

Serious Adverse Device Effect (SADE) – adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Anticipated Serious Adverse Device Effect (ASADE) – serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the risk analysis.

Unanticipated Serious Adverse Device Effect (USADE) – serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the risk analysis.

Figure 12.1.-1: Categorization of All Adverse Events

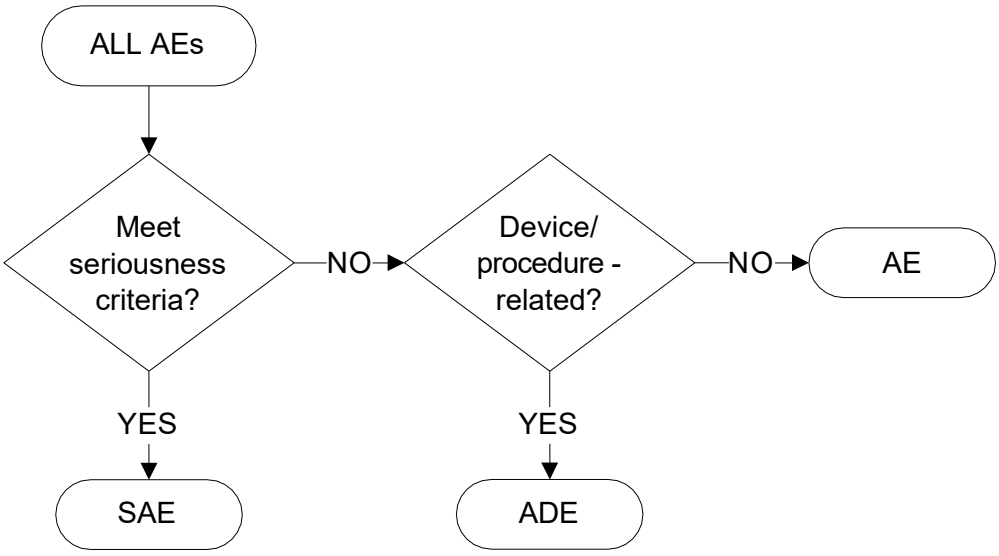
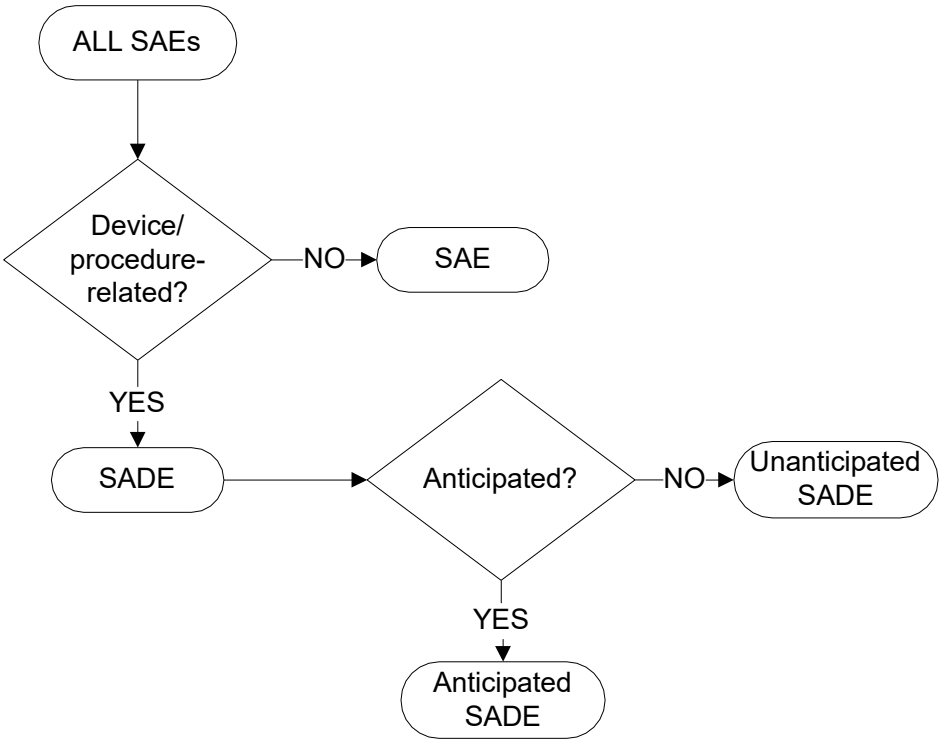


Figure 12.1.-2: Categorization of All Serious Adverse Events



Specific Events Relevant to this Protocol

In addition to reporting all adverse events (serious and non-serious) meeting the above definitions, the investigator must report any occurrence of the following serious adverse events as reported in the previous investigational protocols:

- Pupil ovalization >1 mm
- Hypopyon
- Intraocular infection/endophthalmitis
- Lens dislocation
- Macular edema (diagnosed clinically or confirmed by fluorescein angiography and/or optical coherence tomography)
- Pupillary block
- Hyphema
- Cataract formation
- Retinal detachment or retinal detachment repair
- Synechiae
- Corneal haze if associated with a loss of 2 lines or more (0.2 logMAR or more) of best corrected visual acuity (BCVA) from preoperative baseline
- Any secondary surgical intervention except retinal detachment repair (*e.g.*, iridectomy for pupillary block, IOL repositioning, IOL removal due to inflammation, IOL replacement, and procedures that may be reported as "other")
- Corneal stromal edema (Grade 3)
- Iritis (aqueous cells or flare of Grade 3 or higher)
- Raised IOP requiring treatment
- Loss of 2 lines or more (0.2 logMAR or more) of best spectacle-corrected visual acuity (BCVA) from preoperative baseline

Any other potentially sight-threatening events are also considered serious and have to be reported appropriately by the investigator as delineated in Section 12.2.

12.2. Procedures for Recording and Reporting

All adverse events will be documented on the Adverse Event electronic case report form (eCRF) within the Electronic Data Capture (EDC) system and collected on a routine basis at monitoring visits. Adverse events must be collected from the time of informed consent.

In addition, the investigator must document all ADEs, SAEs, [redacted] with details including the date of occurrence, severity, treatment (if applicable), outcome, and assessments of the seriousness and causality. The site must submit all available information to the study sponsor immediately as follows:

- **ADEs or SAEs are documented on the *Adverse Device Effect and Serious Adverse Event Form* in the EDC system within 24 hours of the investigator's or site's awareness.**
- [redacted]
- **Additional relevant information after initial reporting is to be updated in the EDC system as soon as the data becomes available.**
- **Document any changes to the medical history and concomitant medication on the appropriate forms in the EDC system.**
- **All relevant documentation such as Discharge Summary, Autopsy Report, Certificate of Death etc, should be faxed to the study sponsor at [redacted].**

Note: Should the EDC system become non-operational, the site must complete the appropriate paper *Adverse Device Effect and Serious Adverse Event Form* [redacted] The completed form is faxed to the study sponsor at [redacted] within 24 hours of the investigator's or site's awareness; however, the reported information must be entered into the EDC system once it becomes available.

Study sponsor contact information is provided in Table 12.2.-1.

Table 12.2.-1:
Contact Information for C-09-043

Study Staff	Business Phone	Business Fax
Clinical Trial Manager: [redacted], PhD [redacted]	[redacted]	[redacted]
Clinical Site Management: [redacted]	[redacted]	[redacted]
Medical Monitor: [redacted] MD, MBA, CPE, FAAO [redacted]	[redacted]	[redacted]

Further, depending upon the nature of the adverse events [redacted] being reported, the study sponsor may request copies of applicable portions of the subject's medical records. The investigator must also report all adverse events [redacted] that could have led to a SADE according to the requirements of regulatory authorities or IRB/IEC.

Intensity and Causality Assessments

For every adverse event [redacted], the investigator must assess the causality as Related or Not Related to the medical device or test procedure in the study. An assessment of causality will also be performed by a study sponsor physician utilizing the same definitions, as shown below:

Causality

Related — An adverse event [redacted] classified as related may be either definitely related or possibly related where a direct cause and effect relationship with the medical device or test procedure has not been demonstrated, but there is a reasonable possibility that the adverse event [redacted] was caused by the medical device or test procedure.

Not Related	An adverse event [redacted] classified as not related may either be definitely unrelated or simply unlikely to be related (*i*e, there are other more likely causes for the adverse event [redacted]).

Where appropriate, the investigator must assess the intensity (severity) of the adverse event as mild, moderate, or severe based on medical judgment with consideration of any subjective symptom(s), as defined below:

Intensity (Severity)

Mild	An adverse event is mild if the subject is aware of but can easily tolerate the sign or symptom.
Moderate	An adverse event is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities.
Severe	An adverse event is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

12.3. Unmasking of Study Information

Not applicable; this study is open-label.

12.4. Follow-Up of Safety Information

The investigator is responsible for adequate and safe medical care of subjects during the study and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the study. The investigator should provide the sponsor with any new safety information (which includes new adverse events and changes to previously reported adverse events) that may affect the safety evaluation of the device. Any additional data from these follow-up procedures performed up to 6 months after subject exit must be documented and available upon the study sponsor's request.

13. REGULATORY AND ETHICAL COMPLIANCE

This clinical trial will be conducted in accordance with the principles of the Declaration of Helsinki, and in compliance with ISO 14155:2011 clinical investigation of medical devices for human subjects, Good Clinical Practice (GCP), Code of Federal Regulations (CFR), Standard Operating Procedures (SOPs) of Alcon and Contract Research Organizations participating in the conduct of the clinical trial, and all other applicable regulations.

14. RESPONSIBILITIES

14.1. Investigator Responsibilities

The Investigator will comply with the commitments outlined in the Statement of Investigator (Form FDA 1572 or Alcon Form CS006). The Investigator and all clinical trial staff will conduct the clinical trial in compliance with this protocol and with GCP and all applicable regulatory requirements. The Investigator will ensure that all personnel involved in the conduct of the clinical trial are qualified to perform their assigned duties through relevant education, training, and experience.

14.2. Sponsor and Monitor Responsibilities

The Sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals. The clinical investigation will be monitored, following the Monitoring Plan, to ensure that: the rights and well being of the patients are protected; the reported data are accurate, complete, and verifiable from the source documents; the equipment used to assess variables in the clinical investigation is maintained and calibrated per manufacturer instructions and Sponsor requirements; the study is conducted in compliance with the current approved protocol (and amendment[s], if applicable), with current Good Clinical Practice (GCP), and with applicable regulatory requirements.

All studies will have a site initiation. Monitoring will be conducted periodically while the clinical study is ongoing. Monitoring methods may include site visits, telephone, written and fax correspondence. The Study Manager and/or the assigned Clinical Site Manager will contact each site at appropriate intervals. The Lead Clinical Site Manager will determine the frequency of site visits. Close-out visits will take place after the last visit of the last patient.

15. CONFIDENTIALITY

The existence of this clinical study is confidential and should not be discussed with persons outside of the study. You shall hold confidential, and not disclose directly or indirectly to any third party other than those persons involved in the study who have a need to know, the protocol, the data arising out of the study, and any other information related to the study or to Alcon's products or research programs that is provided by Alcon to you (the "Confidential Information"). All such persons must be instructed not to further disseminate this information to others. You shall not use the Confidential Information for any purpose other than the study. The foregoing obligations of confidence and non-use assumed by you shall not apply to: (a) information which at the time of disclosure is in the public domain; (b) information which thereafter lawfully becomes part of the public domain other than through disclosure by or through you; (c) information which, as evidenced by your written records, was known by you prior to Alcon's disclosure; (d) information which is lawfully disclosed to you by a third party not under any obligation of confidence to Alcon; or (e) information which is required to be disclosed by law or government regulatory agency, provided reasonable advance notice of such disclosure is given to Alcon.

All data and discoveries arising out of the study, patentable or nonpatentable, shall be the sole property of Alcon, Inc. Alcon reserves the right of prior review of any publication or presentation of information related to the study. Alcon may use these data now and in the future for presentation or publication at Alcon's discretion or for submission to government regulatory agencies.

16. REFERENCES

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17. STUDY PLAN

Table 17.-1:
Study Plan

	Nominal Time ± Visit Window Limits												
	Entrance Visit [a]	Year 4/4A [c]	Year 5/5A [d]	Year 5.5/5.5A	Year 6/6A	Year 6.5/6.5A	Year 7/7A	Year 7.5/7.5A	Year 8/8A	Year 8.5/8.5A	Year 9/9A	Year 9.5/9.5A	Year 10/10A
Procedure / Assessment		Day[b] 1429 – 1550	Day 1794 – 1915	Day 1976 – 2097	Day 2159 – 2280	Day 2341 – 2462	Day 2524 – 2645	Day 2706 – 2827	Day 2889 – 3010	Day 3071 – 3192	Day 3254 – 3375	Day 3436 – 3557	Day 3619 – 3740
Informed Consent	X												
Inclusion/Exclusion	X												
Enrollment Information[e]	X												
Medical History	X												
[redacted]													
Central [redacted] Endothelial Cell Photography-3 images each		X	X	X	X	X	X	X	X	X	X	X	X
[redacted]													

[redacted]

Adverse Events (both volunteered and elicited)	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 Year 4 or later (*i.e.*, Year 4, 5, 5.5, 6, 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.

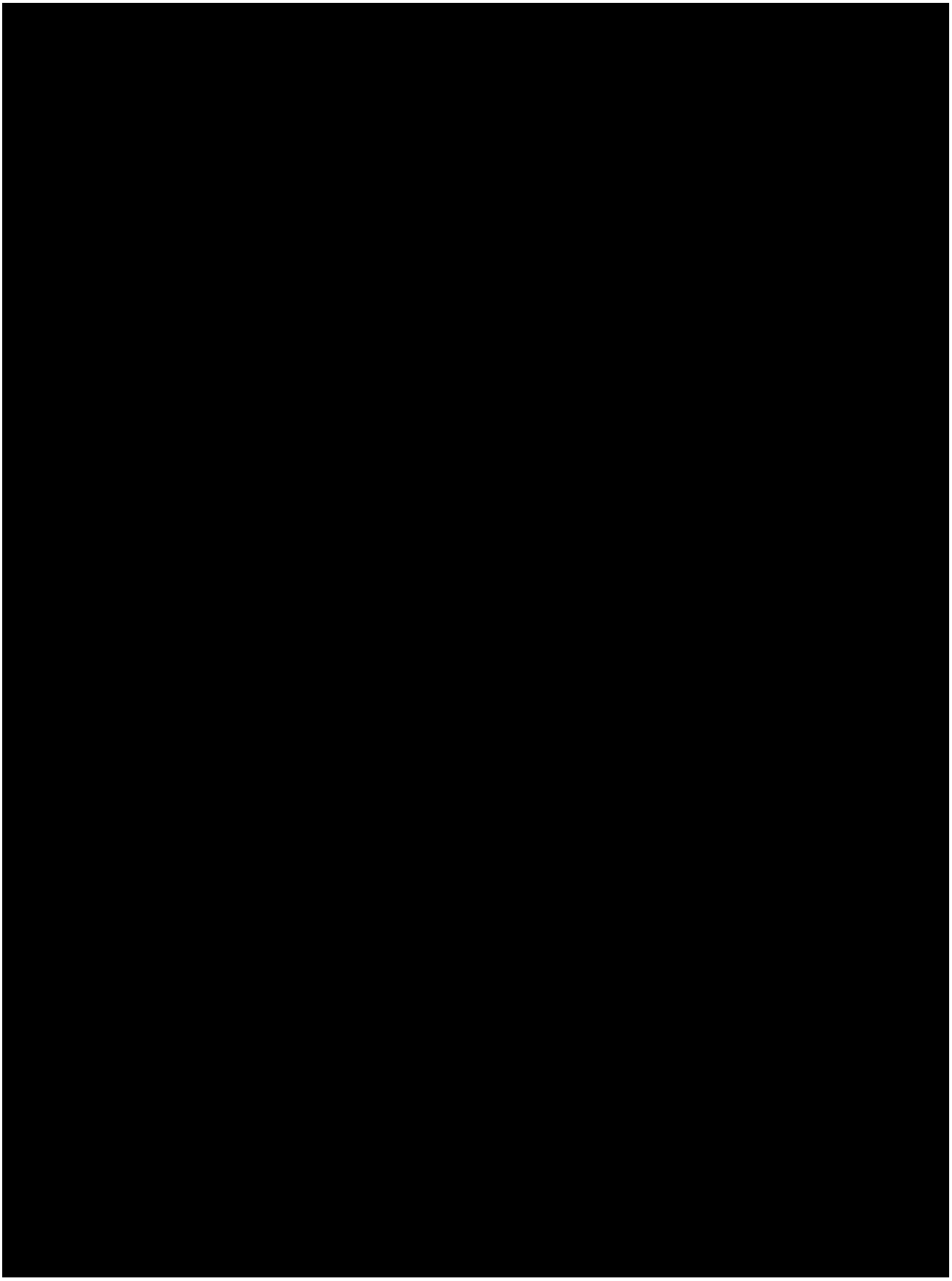
[c] Data from subject's 2nd implant surgery will be captured on Forms designated with an "A".

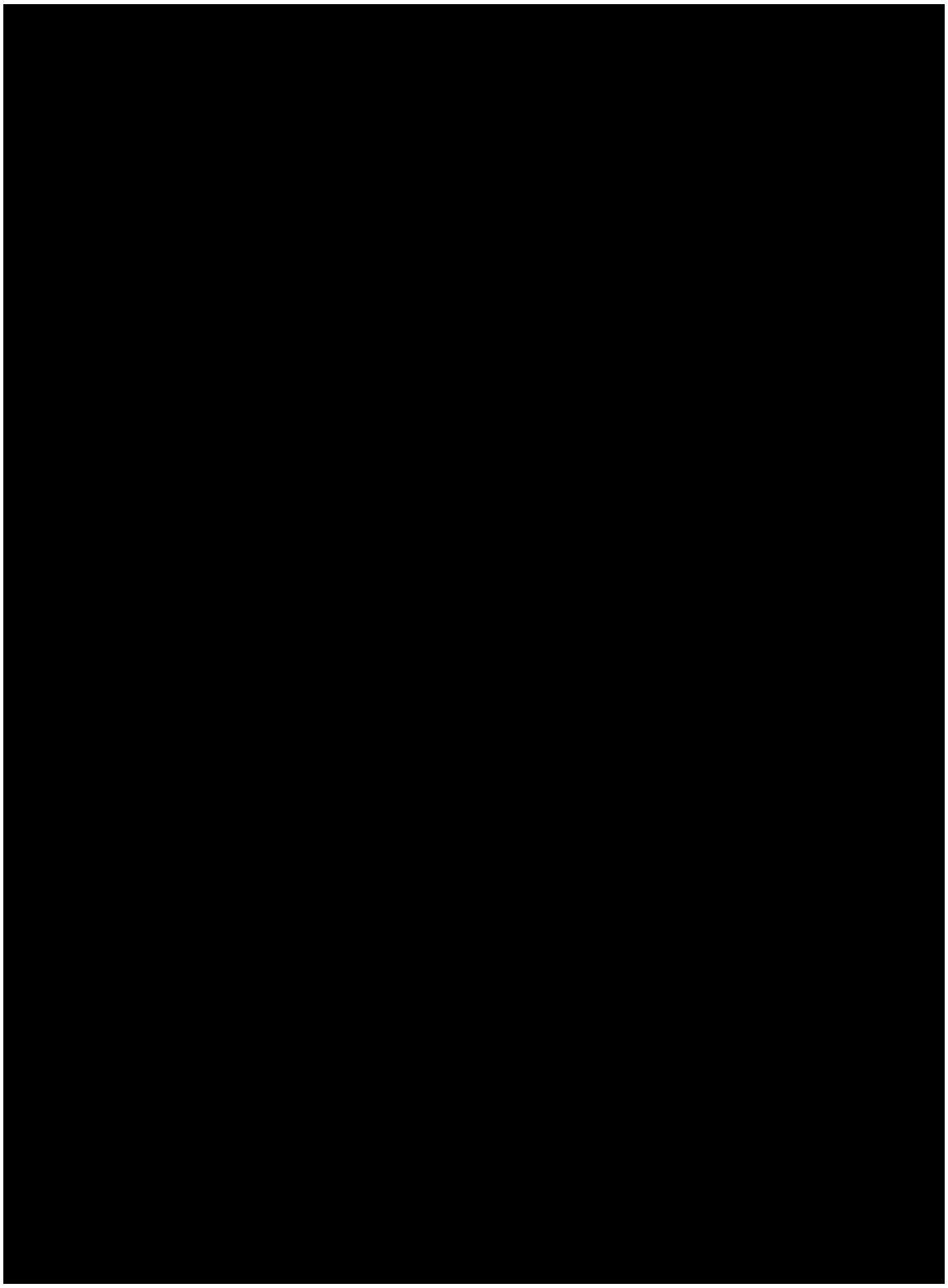
[d] A 4.5 Year visit is not included since all patients are past this time-point.

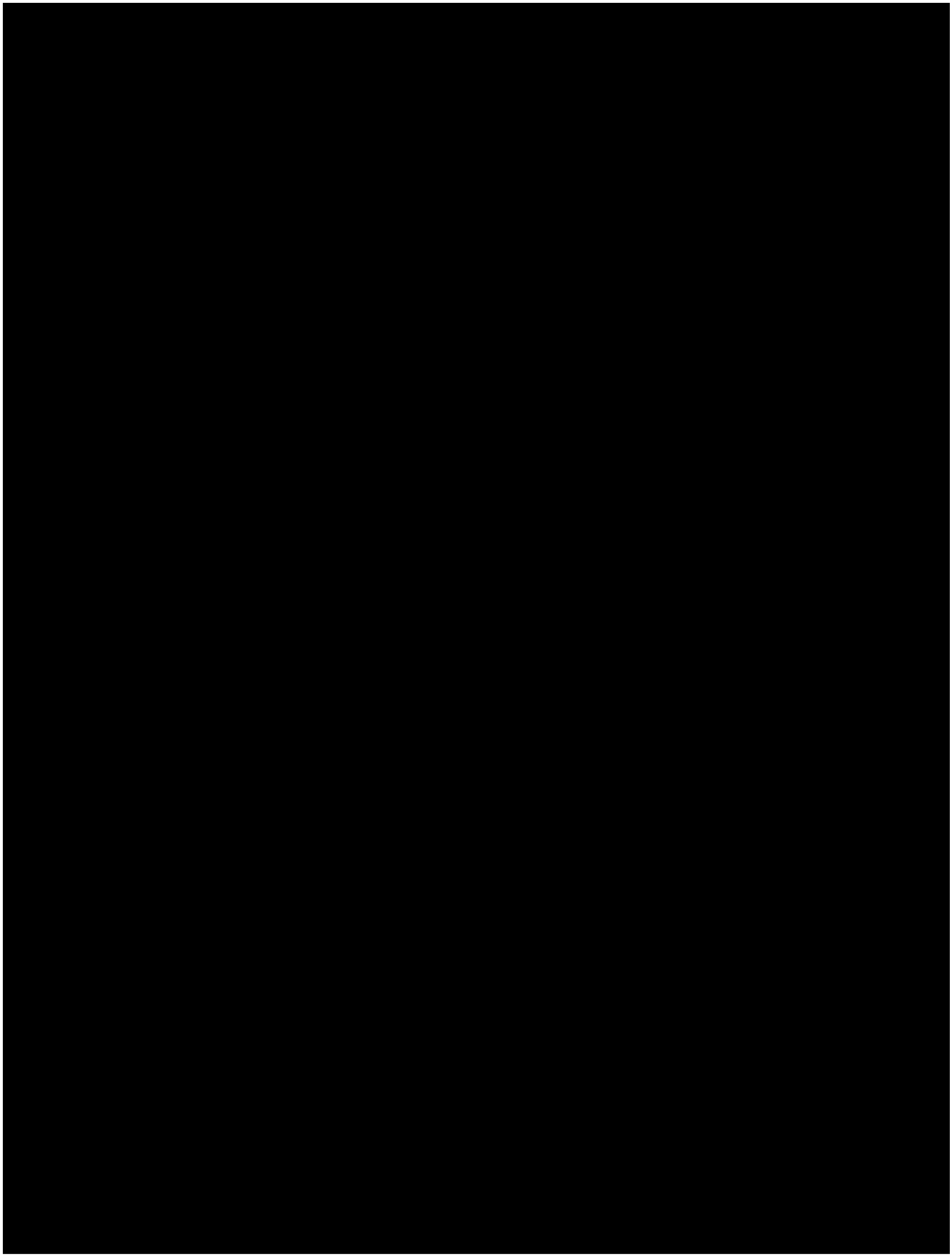
[e] The Enrollment Information panel will collect basic information from the subject's previous study (*e.g.*, protocol number, investigator number, subject number, and the first Form/Visit where data is captured in this study for each eye).

[redacted]

[redacted]







Approval Page
Safety Protocol for ACRYSOF CACHET Phakic Lens

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
04/17/2013 01:03:55	[redacted]	Clinical Medical Monitor
04/17/2013 18:40:57	[redacted]	Biostatistics
04/17/2013 21:40:36	[redacted]	Product Safety
04/18/2013 16:15:19	[redacted]	Clinical Study Manager