Post-Market Clinical Follow-up Study—Retrospective Evaluation of Endothelial Cell Density and IOL Explants Related to the Clinical Use of AcrySof® CACHET® Phakic Lens in Three European Countries

Study Protocol, Version 2.0

[redacted]

[redacted] [redacted]

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[redacted]	[redacted]
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[redacted]

[redacted]

ABBREVIATIONS

ANSM	French Health Products Safety Agency (Agence nationale de sécurite du médicament et des produites de santé)
CI	confidence interval
DSEK	Descemet's stripping endothelial keratoplasty
ECD	endothelial cell density
ECL	endothelial cell loss
IOL	intraocular lens
RTI-HS	RTI Health Solutions
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

POST-MARKET CLINICAL FOLLOW-UP STUDY: PROTOCOL OUTLINE

Title	**Post-Market Clinical Follow-up Study—Retrospective Evaluation of Endothelial Cell Density and IOL Explants Related to the Clinical Use of AcrySof® CACHET® Phakic Lens in Three European Countries**
Rationale	Corneal endothelial cells pump excess fluid from the corneal stroma to maintain the water balance required for transparency. Corneal endothelial cells do not regenerate; wound healing occurs by adjacent cells changing their shape or size. Phakic anterior chamber implants are used for the correction of myopia or hypermetropia, using angle-supported or iris fixation techniques. The loss of endothelial cells of the cornea involving phakic anterior chamber implants from different manufacturers has been reported [redacted] in the past; in some cases, this has led to explants and corneal grafts after 2-3 years of implantation. This [redacted] study [redacted] will [redacted] provide data on endothelial cell density and explants in [redacted] a real-life clinical setting.
Objectives	The primary goals of the study are to capture data on endothelial cell density in actual practice [redacted] and to quantify the frequency of endothelial cell loss (ECL) and AcrySof® CACHET® Phakic Lens explants.
Source Populations	The study will be implemented in France, Germany, and Spain.
Previous Research	[redacted] The threshold for ECL [redacted] is defined as endothelial cell density (ECD) < 1,500 cells/mm^2 or > 30% loss from preoperative baseline. Two types of ECL are [redacted] defined: acute (due to surgical trauma, onset at or before the 6-month visit) and chronic (onset after the 6-month visit). Of 1,323 eyes from previous clinical studies, 50 (3.8%) met the threshold for ECL within 3 or 5 years postoperative follow-up [redacted]: ▪ 26 eyes (2.0%) with an onset at or before the 6-month visit ▪ 24 eyes (1.8%) with an onset after the 6-month visit
Study Design	Retrospective cohort study of implanted patients between 2008 and 2013. Information from patient medical records will be collected through an online electronic data capture platform specifically

	constructed for the use of the treating surgeons (one file per implanted eye). Preoperative data (demographics, ECD measurements and other relevant characteristics) and postoperative data (ECD measurements and explants information) will be abstracted.
Study Cohort	Patients implanted with an AcrySof® CACHET® Phakic Lens by a surgeon selected into this study and willing to participate.
Inclusion Criteria	Subjects implanted with AcrySof® CACHET® Phakic Lens
Exclusion Criteria	None
Follow-up	Until study end
Outcome	The primary outcomes of interest in this study are (1) the variation over time, of ECD from the implant date, measured as a continuous variable, (2) decreases in ECD that are perceived to put at risk endothelial cell function (aggregated as ECL), and (3) the explant of the AcrySof® CACHET® Phakic Lens. [redacted]
Other Variables of Interest: Patient Characteristics, Comorbidities of Interest	Demographics, comorbidities, selected life-style factors and comedications (systemic and ophthalmic)
Study Size	Recruitment target: 200 patients (200-400 eyes)
Statistical Analysis	▪ Mean and standard deviation (or median and interquartile range) of ECD in the preoperative visit and monthly after surgery ▪ Counts of operated eyes and percentage with each outcome, with the corresponding 95% confidence intervals ▪ Longitudinal analysis of ECD and ECL, including Kaplan-Meier curves of cumulative ECL
Ethical and Scientific Review Procedures	Institutional review board approval and/or any other required reviews of the study protocol by specific committees will be obtained in accordance with applicable national and local regulations. The study will be conducted in accordance with the *Guidelines on Medical Devices—Post-Market Clinical Follow-Up Studies: A Guide For Manufacturers and Notified Bodies* (European Commission, January 2012); International Society for Pharmacoepidemiology (ISPE) (2007) *Guidelines for Good Pharmacoepidemiology Practices (GPP)*;

	and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2012). The ENCePP *Checklist for Study Protocols* (ENCePP, 2013) will be completed, and the study will be registered in the ENCePP study registry (ENCePP, 2010).
Adverse Event Reporting	The study will collect de-identified information from patients' medical records via a structured case report form. We do not anticipate collecting information on adverse events (serious and non-serious) and device deficiencies other than the study outcomes, but we encourage the investigators to report any adverse event related to the medical device and device deficiencies to the sponsor immediately. All suspected adverse events and device deficiencies reported during the study will be reviewed by the sponsor's medical safety department as per MEDDEV 2.12-1 rev.8 on Medical Devices Vigilance system, and will be reported to each country's Competent Authority following European and Local legislations (European Commission, March 2012).
Regulatory Communication Plan	Study protocol, study status, and reports will be included in regulatory communications in line with regulatory milestones and requirements.
Publication and Communication Plan	Any publication of study results will be published following the International Committee of Medical Journal Editors (2010) guidelines, and communication in appropriate scientific venues, e.g., ISPE conferences, will be considered. The appropriate STROBE checklist (STROBE, 2007) for study reporting will be followed.

AMENDMENTS AND UPDATES

Version 2.0 (May 31, 2013). Updates of sections: Setting (recruitment), Variables, Data Management (specified data entry system), Quality Control (more detail), Management and Reporting of Adverse Events.

Version 1.0, 19 July 2012.

1 RATIONALE AND BACKGROUND

Corneal endothelial cells pump excess fluid from the corneal stroma to maintain the water balance required for transparency. Corneal endothelial cells do not regenerate, and wound healing occurs by adjacent cells changing their shape or size.

Endothelial cell density (ECD) decreases with age at a rate of 0.6% (±0.5%) per year (Bourne et al., 1997). Average measurements for ECD are: in children, 4,000 cells/mm^2; in middle-aged adults (30 years), 2,700 to 2,900 cells/mm^2; and among adults aged older than 75 years, 2,400 to 2,600 cells/mm^2 (McCarey et al., 2008). As a consequence of low endothelial cell count, corneal edema may result which may cause clouding of the cornea and blurred vision. This occurs when ECD is 400-700 cells/mm^2 (Edelhauser, 2006). The treatment for a cloudy cornea is either a full corneal transplant or Descemet's stripping endothelial keratoplasty (DSEK).

Phakic anterior chamber implants are used for the correction of myopia or hypermetropia, using angle-supported or iris fixation techniques. The loss of corneal endothelial cells after phakic anterior chamber implants [redacted] has been reported [redacted] in some cases, this has led to explants and corneal grafts after 2-3 years of implantation. [redacted]

During clinical studies, [redacted] 1,323 eyes [redacted] of patients are being followed for safety for up to 10 years after surgery. [redacted] In 5 years of postoperative follow-up, there were 12 [redacted] total explants, of which 4 (0.3%) were due to ECL. [redacted]

The threshold for ECL was defined as endothelial cell density (ECD) < 1,500 cells/mm^2 or > 30% loss from preoperative baseline. Two types of ECL were defined: acute (due to surgical trauma, onset at or before the 6-month visit) and chronic (onset after the 6-month visit).

Of 1,323 eyes from previous clinical studies, 50 (3.8%) met the threshold for ECL within 3 or 5 years postoperative follow-up [redacted].

- 26 eyes (2.0%) with an onset at or before the 6-month visit
- 24 eyes (1.8%) with an onset after the 6-month visit

This [redacted] study will complement [redacted] development project findings with data on ECD and explants in the clinical setting.

2 RESEARCH QUESTION AND OBJECTIVES

The goals of the study are to evaluate ECD data in a real-life clinical practice setting and to quantify the frequency of ECL and AcrySof® CACHET® Phakic Lens explants.

3 RESEARCH METHODS

3.1 Study Design

In this cohort study, subjects will be followed from their last preoperative visit with an ECD measurement to the most recent postoperative visit. Information will be collected from patient medical records through an online electronic data capture platform specifically constructed for the use of the treating surgeons (one file per implanted eye), in which preoperative (demographics, ECD measurements and other relevant characteristics) and postoperative data (ECD measurements, explants) will be abstracted.

3.2 Setting

The study will be implemented in France, Germany, and Spain. In each country, a lead investigator will be recruited to centralise and help organise the research effort in the country, and a contract research organisation specialised in data collection will handle the contact with the local surgeons.

It is expected that a proportion of the variability in the ECD measurements will be associated with the equipment used to measure ECD and the personnel who operates the equipment. For this reason, [redacted] centres with a minimum of 50 lenses implanted each—representative of regular AcrySof® CACHET® Phakic Lens users—will be randomly selected. [redacted]

In all countries, sites will be selected from Alcon's lists; in Germany and Spain, two ophthalmology centres with at least 50 lenses implanted will be randomly selected. [redacted]

[redacted] In France, with a lower number of implants, three sites will be randomly selected from among the 5 centres with the highest number of implanted lenses. [redacted] Surgeons will be requested to provide information on all their patients with at least one eye implanted with an AcrySof® CACHET® Phakic Lens. It is possible that the number of patients slightly exceeds the target number of 200. In terms of follow-up, we will require that patients have at least one postoperative visit (with ECD measurements or otherwise) to be able to collect information on all study outcomes of interest, including very early ones.

The source of information for the study will be the medical records of patients who were implanted with an AcrySoft® CACHET® Phakic Lens at each site.

At each site, the physician investigator and co-investigators (where applicable) will be asked to abstract data from the medical records of all patients who had an AcrySoft® CACHET® Phakic Lens implanted. Physicians will not be required to contact patients to obtain information on study variables that are not recorded in the patients' records.

3.3 Variables

3.3.1 Outcomes

Clear vision largely depends on the cornea being transparent. When liquid is retained in the cornea (corneal edema), vision becomes blurry. The corneal endothelial cells remove liquid from the corneal stroma. There is a consensus that, when the ECD decreases below a threshold, endothelial cell function may be impaired and liquid may accumulate. The density of endothelial cells decreases with age, and the speed of the decrease can be modified by trauma, disease, or chemical toxicity. ECD at a given age also varies by ethnicity (McCarey et al., 2008). Therefore, the primary outcomes of interest in this study are (1) variation of ECD over time from the implant date, measured as a continuous variable; (2) decreases in ECD that are perceived to put at risk the endothelial cell function (aggregated as ECL); and (3) explant of the AcrySof® CACHET® Phakic Lens:

[redacted]

[redacted]

3.3.2 Outcome Assessment

Endothelial cell density is measured by corneal endothelial specular microscopy. There are several models of specular microscopes in ophthalmology clinics, and the quality or variability of the measurements may be related to the equipment used or the technician operating it. To decrease variability, the usual technique involves measuring the density in several corneal images. Ideally, and because central and peripheral endothelial cell densities may decrease at varying speeds, three central and three peripheral measurements should be taken and combined. However, in a real-world setting, not all measurements may be available.

The data collection form will have fields for three central and three peripheral measurements per visit, as well as for information on the equipment used and de-identified information on the technician responsible for the measurement.

3.3.3 Covariates

Surgeons will be asked to abstract the following data from the medical records of each of their patients/eyes who were implanted with an AcrySof® CACHET® Phakic Lens and introduce the data in the electronic data capture system developed for the study:

- Surgeon's pseudo-ID
- Centre pseudo-ID where the surgery took place
- Date of the surgery
- Description of any problem that occurred around or during surgery
- Eye operated upon (left or right)
- AcrySof® CACHET® Phakic Lens model and size
- Patient's age at the time of surgery
- Patient's sex
- Medical conditions (prior to the surgery)
  - Systemic (diabetes mellitus, type 1 and type 2, seasonal allergies)
  - General eye diseases/conditions (chronic ocular inflammation, ocular herpes zoster, ocular herpes simplex, dry eye, collagen disorders, immunodeficiency disorders)
  - Corneal diseases/conditions (Fuch's dystrophy, posterior polymorphous dystrophy, congenital hereditary corneal dystrophy, iridocorneal endothelial syndrome, anterior segment dysgenesis)

  - Ocular trauma and surgeries (same eye)(previous ocular trauma, previous ocular refractive surgery, other previous ocular surgery)
- Concomitant medications (carbonic anhydrase inhibitors, prolonged use of ophthalmic solutions containing benzalkonium chloride, topical corticosteroids, topical NSAIDs [nonsteroidal anti-inflammatory drugs], topical anesthetics)
- Last preoperative visit with ECD measurement (per implanted eye):
  - Best corrected visual acuity
  - For each measurement of ECD:
    - Date of ECD measurement
    - Eye evaluated
    - Type of equipment used or method of measurement
    - Technician (identified by an assigned code, not by name or personal information)
      - Endothelial cell analysis, for up to three images for the central area and up to three images for the peripheral area: each image's density (cells/mm^2), number of cells analyzed and image status (photograph OK, no photograph or < 100 countable cells)
- Each postoperative visit (per implanted eye):
  - Best corrected visual acuity
  - For each measurement of ECD:
    - Date of ECD measurement
    - Eye evaluated
    - Type of equipment used or method of measurement
    - Technician (identified by an assigned code, not by name or personal information)
    - Endothelial cell analysis, for up to three images for the central area and up to three images for the peripheral area: each image's density (cells/mm^2), number of cells analyzed, and image status (photograph OK, no photograph, or < 100 countable cells)
    - If the AcrySof® CACHET® Phakic Lens was explanted or repositioned, information on date of surgery(ies), reason(s) for surgery(ies), and whether a corneal transplant was performed post explant

3.4 Study Size

The target is 200 patients total, who will contribute 200-400 eyes to the study. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.5 Data Management

The INTrial (2013) electronic data capture system developed by Kantar Health will be used to collect patient data. INTrial is an online electronic data capture platform for data entry, data validation, and data management in clinical studies, which has been successfully used in numerous national and international studies for over 10 years and which provides a comprehensive suite of frontend and backend solutions. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

The use of the electronic data capture technology minimizes the burden on the physician and the site and maximizes the quality of the data while ensuring that participant privacy is maintained throughout the process. Using an electronic data capture system will improve data collection efficiency, decrease response error, and facilitate physicians' contribution. However, if some sites are anticipated to have limited access to a computer, a pen-and-paper CRF option could also be considered.

Data collection will be performed by physicians or designated site support staff through the abstraction of data from the patients' medical records from the time of the preoperative visit through the last postoperative visit with available data of interest to the study.

3.6 Data Analysis

The data analysis will be performed by analysts at RTI Health Solutions (RTI-HS).

[redacted]

3.6.1 Descriptive Analysis of Covariates

The descriptive analysis of these data will include tables to show the distribution of the variables of interest (n and percentage for binary and categorical variables; mean and standard deviation, or median and interquartile range for continuous variables) selected from the information collected in the questionnaires. Tables will be stratified by the presence of the outcome.

The unit of analysis will be the ophthalmology center, the subject, or the operated eye, as appropriate for each characteristic.

3.6.2 Summary of Outcomes

The mean and standard deviation (or median and interquartile range) of ECD at the last preoperative visit and each month after surgery (e.g., days 1 through 30; 31 through 60), using information from postoperative visits during those intervals, will be provided. Counts and percentages, with the corresponding 95% confidence intervals, of [redacted] acute ECL, chronic ECL, explant of AcrySof® CACHET® Phakic Lens ≤ 6 months after implant, and explant of AcrySof® CACHET® Phakic Lens > 6 months of implant.

The unit of analysis will be operated eyes.

3.6.3 Longitudinal Analysis

Kaplan-Meier estimates of cumulative ECL will be provided as graphics. Point estimates of the proportion of subjects who experienced the outcome at months 3 and 12 with two-sided 95% confidence intervals will be provided. These summaries will treat eyes from the same subject as independent observations. Eyes that have been explanted before reaching the predefined ECD levels will be considered censored at the time of explant, but a sensitivity analysis will be reported with these subjects considered as events.

[redacted]

3.7 Quality Control

Standard operating procedures will guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

At RTI-HS, an independent Office of Quality Assurance will perform audits and assessments that involve various aspects of the project. Such audits will be conducted by the Office of Quality Assurance according to established criteria in standard operating procedures and other applicable procedures.

[redacted]

A quality-assurance audit of this study may be conducted by the sponsor or the sponsor's designees.

Appropriate data storage and archiving procedures will be followed (i.e., storage on CD-ROM and DVD), with periodic backup of files to tape. Standard procedures will be in place to restore files in the event of a hardware or software failure.

3.8 Limitations and Strengths of the Research Methods

To decrease surgeon-related variability, we will involve as few surgeons as possible. As a result, surgeons who have more patients with implants will be preferred. It is possible that these surgeons have lower proportions of undesired events such as ECL; therefore, the proportions we will estimate may not be fully generalisable to all surgeons implanting these lenses.

4 PROTECTION OF HUMAN SUBJECTS

[redacted] This is a non-interventional study; therefore, the risks for patients linked to their participation in the study are limited to a breach of confidentiality with regard to personal identifiers or health information. The study will collect de-identified information from patients' medical records without any involvement or participation of patients. Therefore, we anticipate that no patient informed consent will be required. Independent ethics committee approval (as required) will be according to the guidance of each country's research ethics requirements; and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)

The study will be conducted under the following guidelines:

- Guidelines on Medical Devices—Post-Market Clinical Follow-Up Studies: A Guide For Manufacturers and Notified Bodies (European Commission, January 2012)
- Guidelines for Good Pharmacoepidemiology Practices (GPP). International Society for Pharmacoepidemiology; 2007. Available at: http://www.pharmacoepi.org/resources/guidelines_08027.cfm. Accessed April 19, 2013.
- Guide on Methodological Standards in Pharmacoepidemiology (ENCePP, 2011).

The study will comply with the definition of the non-interventional (observational) study provided the 2012 Guideline on Good Pharmacovigilance Practices (GVP): Module VIII – Post-Authorisation Safety Studies (EMA, 2012). The study will comply with the nature of non-interventional (observational) studies referred to in the ICH harmonised tripartite guideline Pharmacovigilance Planning E2E (ICH, 2004).

RTI holds a Federal-Wide Assurance (FWA #3331 effective until June 17, 2014) from the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) that allows us to review and approve human subjects protocols through our IRB committees. These committees are also registered with OHRP for both DHHS- and FDA-regulated research (registration expires June 23, 2014). Our FWA requires IRB review for all studies conducted by RTI that involve human subjects, regardless of the funding source. Depending on the level of risk and nature of the research, a study may be ruled as exempt from IRB review by an IRB chair or designated IRB member. We plan to apply for an exemption. These IRBs have been audited by the FDA and are fully compliant with applicable regulatory requirements. The committees review research studies to ensure adherence to appropriate regulations that govern human subjects research, including 45 CFR 46, 21 CFR 50 and 56, and with all applicable International Conference on Harmonization provisions. All studies involving human subjects undergo a continuing IRB review at least once per year.

5 MANAGEMENT AND REPORTING OF EVENTS

5.1 Definitions

Device Deficiency

Any alleged inadequacy related to the identity, quality, durability, reliability, safety, effectiveness,, or performance of a device after it is released for distribution.

Note: This definition includes malfunctions, use errors, and inadequate labeling.

Malfunction

A malfunction is a failure of the device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the

labelling for the device. A malfunction should be considered reportable if a serious adverse event has occurred or could occur as a result of a recurrence of the malfunction.

Adverse Event

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 medical device.

Serious Adverse Event (SAE)

Adverse event that led to any of the following:

- Death.
- A serious deterioration in the health of the subject that either resulted in:
  a) A life-threatening illness.
  b) Permanent impairment of a body function or permanent damage to a body structure.
  c) A condition necessitating medical or surgical intervention to prevent a) or b)

  Examples: – Clinically relevant increase in the duration of a surgical procedure,
  – A condition that requires hospitalization or significant prolongation of existing hospitalization
  d) Any indirect harm as a consequence of incorrect diagnostic test results when used within manufacturer's instructions for use.
  e) Fetal distress, fetal death, or a congenital abnormality or birth defect.

5.2 Recording and Reporting Adverse Events and Device Deficiencies

The study will collect de-identified information from patients' medical records via a structured case report form. We do not anticipate collecting information on adverse events (serious and nonserious) and device deficiencies other than the study outcomes, but we encourage the investigators to report any adverse event related to the medical device and device deficiencies to the sponsor.

All suspected adverse events and device deficiencies reported during the study will be reviewed by the sponsor's medical safety department as per MEDDEV 2.12-1 rev.8 on Medical Devices Vigilance system, and will be reported to each country's Competent Authority following European and local legislations.

As this is a retrospective cohort study, the date of awareness of the event will be considered the date when the sponsor learned about the adverse event and/or device deficiency.

6 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

[redacted]

Any study result publication will follow the International Committee of Medical Journal Editors (2010) guidelines, and communication in appropriate scientific venues, e.g., International Society for Pharmacoepidemiology conferences, will be considered.

When reporting results of this study, the checklist entitled Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (2007) will be followed.

7 OTHER GOOD RESEARCH PRACTICE

The study will be conducted in accordance with *Guidelines on Medical Devices—Post-Market Clinical Follow-Up Studies: A Guide For Manufacturers and Notified Bodies* (European Commission, January 2012); the International Society for Pharmacoepidemiology (2007) *Guidelines for Good Pharmacoepidemiology Practices (GPP)*; and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2012).

The ENCePP *Checklist for Study Protocols* (ENCePP, 2013) will be completed, and the study will be registered in the ENCePP study registry (ENCePP, 2010).

8 REFERENCES

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Annex 1. ENCePP Checklist

ENCePP Checklist for Study Protocols (Revision 2)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	9
1.1.2 End of data collection[2]	☒	☐	☐	9
1.1.3 Study progress report(s)	☒	☐	☐	9,22
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results	☒	☐	☐	9

Comments:

The registration in the EU PAS register is mentioned on page 22.

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7,10
2.1.2 The objectives of the study?	☒	☐	☐	7,11
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7,11-12
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 if applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

All study participants will have been implanted with the device that is the object of this study. There is no specific exposure or hypothesis under evaluation.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	7,8,11
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	8,12,13
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	8,17-18

Comments:

All study participants will have been exposed to the device that is the object of this study. Thus, no “measure of effect” related to the device will be estimated. We answered 3.3 with regards to the planned descriptive analyses and to the study of other risk factors for the outcome.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	7,11,12
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	7
4.2.2 Age and sex?	☐	☒	☐	
4.2.3 Country of origin?	☒	☐	☐	7,11,12
4.2.4 Disease/indication?	☒	☐	☐	7-8,11,12
4.2.5 Co-morbidity?	☐	☒	☐	
4.2.6 Seasonality?	☐	☒	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	11,12

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	☒	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	8,12,13,17, 18

Comments:

The device that is the object of this study is AcrySof® CACHET® Phakic Lens. As all study subjects will have been implanted with it, there is no "exposure" under study. However, time since implant (Question 5.5) is a quantity of interest.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	8,12-13,17
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	11,13

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐		17
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

As there is no specific exposure under study, no confounders or effect modifiers can be evaluated. However, some potential risk factors will be explored. We answered Question 7.1 with this in mind.

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	7-8,11,12
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	7-8,11-13
8.1.3 Covariates?	☒	☐	☐	7,11-13
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	13
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	13,14
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	13,14
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	14-16

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	17-18
10.3 Are descriptive analyses included?	☒	☐	☐	17
10.4 Are stratified analyses included?	☒	☐	☐	17
10.5 Does the plan describe the methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☒	☐	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	16,17,19
11.3 Are methods of quality assurance described?	☒	☐	☐	18,19
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	22

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☐	☒	☐	
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	14-15
12.3 Does the protocol address other limitations?	☒	☐	☐	19

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/ Institutional Review Board approval been described?	☒	☐	☐	8,9,19-20
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	19

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	9

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	9,22
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	9,22

Comments:

Name of the main author of the protocol: Alejandro Arana

Date: 15/Nov/ 2013

Signature: [redacted]