Feasibility Study of Compensation for blindness with the PRIMA system in patients with dry age related macular degeneration

Study Acronym: PRIMA-FS

Protocol Number: CIP-PRIMA FS-M

Revision History

Version Date	Changes
CPP2_Rev0	Initial version
CIP-PRIMA FS-M Rev1	• The protocol number has been changed according Pixium's new numbering system • 1 day and 1 week safety examinations are introduced after ANSMs request • The use of silicone oil and retinal coagulation is now optional and only used if the surgeon sees high risk of retinal detachment or bleeding respectively. The product name in case silicone oil will be used is introduced into protocol after ANSMs request. • Laser treatment has been removed from the surgical procedure. • A PRIMA implant with 378 electrodes is now available • Literature is updated • A more detailed description of the Clinical Event Committee was introduced after ANSMs request • A phased enrolment was introduced after ANSMs request • The inclusion criteria were changed after ANSMs request and updated product version • Binocular visual field is introduced as safety measure. • The surgical method by a clearer indication where the implant is placed after ANSM request • To reduce the effect of the surgery the preferred retinal location measured by microperimetry will be avoided for the retinotomy • A description of the tuning and training procedures was introduced after ANSMs request • A home use record to document the use of the device at home is introduced • The system log is described in section 8.1.8 after ANSMs request • A short description of a possible explantation is introduced after CPPs request • The purpose of the interim analyses has been described after ANSMs request. • Minor change in wording has been done in the protocol for better understanding • List of risk is updated

CIP-PRIMA FS-M Rev2	• After early device failure the PRIMA device will be explanted
CIP-PRIMA FS-M Rev3	• Visual acuity test was added as a new secondary endpoint and changes were performed throughout the protocol. A new Appendix C3 & C3A were created to capture the data. The corresponding display calibration is described in the new added App. G7 & G7A • Appendix A updated with new visual acuity test • CRF Appendix D18 new added for acuity test • App. C1 & C1B Octopus visual field test only minor clarification changes performed • Appendix C2A Home use record only minor clarification changes performed

Protocol Signature Page

Protocol Title: Feasibility Study of Compensation for blindness with the PRIMA system in patients with dry age related macular degeneration
Protocol Number: CIP-PRIMA-FS
Version Date: 19 June 2019

The study will be conducted according to the European Standard ISO 14155: 2011 (Clinical Investigation of Medical Devices for Human Subjects), Declaration of Helsinki, MEDDEV 2.7.1 rev 4, Standards of Good Clinical Practice, as defined by the International Conference on Harmonisation and all applicable regulations.

I have read the Clinical Investigation Plan mentioned above and agree to adhere to its requirements.

I have received a copy of the most current version of the Investigator's Brochure.

I will provide copies of the Protocol and access to all information furnished by Pixium Vision SA ("Sponsor") to the study personnel under my supervision and involved in carrying out the study. I will discuss this material with them to ensure that they are fully informed about the investigational device and the conduct of the study.

I have read the Confidentiality Statement of this Protocol. The contents of this Protocol may not be used in any other clinical study and may not be disclosed to any other person or entity without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by law or regulation, for example submission to an Ethics Committee; however, I will give prompt notice to the Sponsor of any such disclosure.

Site Name: _____

Printed Name of Principle Investigator: _____

Date: _____

Signature Principle Investigator:

_____

Signature Sponsor:

_____

1. Table of Contents

1. Contents

2. Synopsis

Annotation: This is an open-label, non-randomized multicentre, prospective, first in human clinical trial study. The study evaluates the safety and performance of a newly developed Retinal Implant.

Title:	Feasibility Study of Compensation for blindness with the PRIMA system in patients with dry age related macular degeneration
Study Acronym:	PRIMA-FS
Indication:	Study indicated for patients with advanced dry macular degeneration
Trial Design:	Open-label, non-randomized, multicenter, prospective, first in human clinical trial, safety and performance study
Subject participation duration	Total study duration for each patient is expected to be 36 months
Schedule of Assessments:	Enrolment, implantation, 1 day and 1 week post implantation, silicone oil removal after 4 weeks if silicone oil has been used, 1.5, 3, 6, 12, 18, 24, 36 months follow-up.
Primary Endpoints:	Elicitation of visual perception by electrical stimulation of the PRIMA implant and safety assessment including complication rates at 1 day, 1 week, 1.5, 3, 6, 12, 18, 24 and 36 months after implantation.
Secondary Endpoint:	Visual acuity
Investigational Product:	PRIMA system
Number of Patients:	Up to 5 subjects will be implanted with a PRIMA device. Taking screening failures into account up to 10 subjects can be enrolled in the study.

Study Procedure:	Recruiting, screening, informed consent, implantation, follow up, training sessions, endpoint tests.
Treatment:	Implantation, training and stimulation sessions, endpoint testing at 1.5, 3, 6, 12, 18, 24 and 36 months
Coordinating Investigator:	Dr. Yannick Le Mer
Study Coordination:	Dr. Ralf Hornig
Time Schedule:	First subject enrolled September 2017 Last subject enrolled: June 2018 Last subjects visit: August 2021 Enrolment phase 9 Months Study period: 54 Months

3. General Information

3.1. Protocol

Title: Feasibility study of compensation for blindness with the PRIMA system in patients with dry age related macular degeneration

Protocol Number: CIP-PRIMA_FS

Date: 19 June 2019

Sponsor:

Pixium Vision SA,
Study coordination: Dr. Ralf Hornig

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3.2. Authorized persons

Individual responsible for revising the protocol and submitting amendments is:
Ralf Hornig, Director of Clinical Affairs
Email: rhornig@pixium-vision.com

4. Background Information

4.1. Prima System Overview

PRIMA is manufactured by Pixium Vision SA, and consists of the following assemblies and components (See Figure 1 for schematic description):

- One Retinal Implant loaded in an individual delivery system, in a sterile double package,
- A Visual Processor comprising:
  - A Visual Interface (goggles),
  - A Pocket Processor, its batteries and shoulder strap, worn by the patient over the shoulder,
  - A Battery Charger.

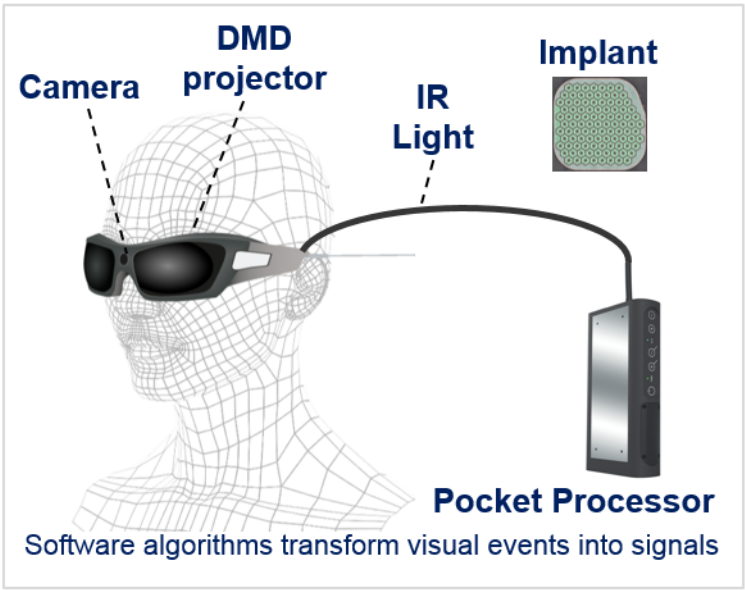


Figure 1: PRIMA System Overview

The PRIMA Bionic Vision System is a device for treatment of patients who have lost their sight through outer retinal degenerative conditions of the eye such as dry age related macular degeneration.

The PRIMA System is designed to provide partial restoration of the patient's visual function through electrical stimulation of the retinal neurons by a sub-retinally implanted stimulator that replace part of the degenerate photoreceptors (see Figure 2)

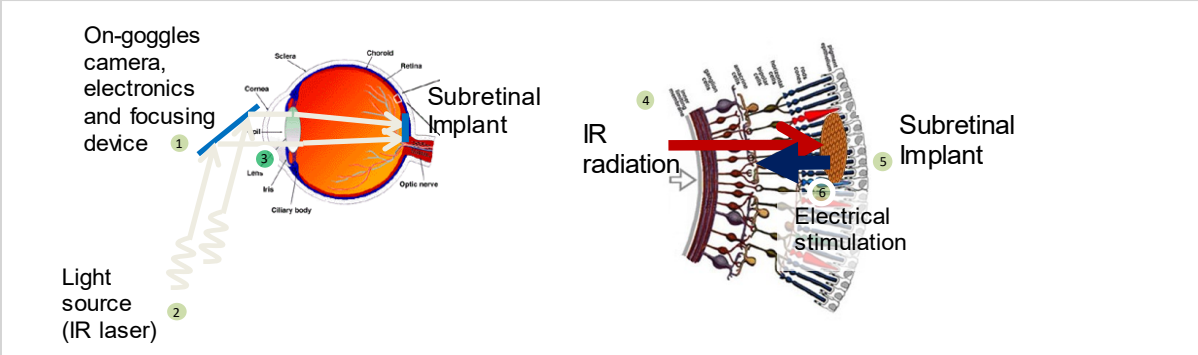


Figure 2: Concept of PRIMA; left: projection of IR patterns in the eye; right: position of implant

The implant converts infrared light into current that then stimulates the inner retinal cells behind which the implant is located.

The interface with the visual environment is achieved through an image sensor integrated in a pair of glasses that captures the overall field of view ("visual scene"). The visual information is then processed and converted to stimulation information which is used to activate the implanted retinal prostheses ("Implants").

Stimulation waveforms of infrared light are projected into the eye, through near-to-eye projection system. When the gaze direction is such that some part of the implant is illuminated by part of the stimulation data, the photovoltaic Retinal Implant converts that part of the signal into electrical current that stimulates the retina accordingly.

The implant consists of photovoltaic cells that are each connected to a stimulation electrode. A photovoltaic cell combined with electrode is referred to as a pixel. The implant has 378 pixels, each 100 µm in diameter. Whenever the projected infrared light illuminates a photovoltaic cell the connected electrode stimulates the adjacent retinal nerve cells electrically. If the implant is illuminated with an infrared pattern, then the stimulation will be also patterned and the patient should perceive this pattern.

4.2. Study concept

In this study, the principle functionality of the device will be tested in humans for the first time. The study will evaluate the extent to which patients with dry age related macular degeneration (AMD) have evoked light perception using the implant.

4.3. Nonclinical (pre-clinical) and Clinical Findings

4.3.1 Pre-clinical Data

The preclinical findings include data and reviews related to biological, product performance and safety testing of device. The pre-clinical data is contained within the Investigators Brochure Section 12.

4.3.2 Clinical Data

Chow 2004 implanted the Optobionics Artifical Silicon Retina MPDA, with approximately 5000 photodiodes in a passive array, into the right eyes of 6 patients suffering from RP. The implant was very similar to the study device of protocol at hand but no external components were available. Follow up periods ranged from 6 to 18 months. There was no evidence that the photodiodes produced sufficient signal in response to light from ordinary visual images on the retina to stimulate interneurons and communicate patterned visual information to the CNS. However, there were some visual function improvements. **Chow 2010** later reported about 4 additional patients with similar results. **Del Priore 2005** and **Rizzo 2011** discuss this work, and conclude that these were due either to post-surgical retinal sparing or examiner bias (the study design had no elements of blinding or randomisation). **Weiland 2011** reviews conference papers reporting on extension of this study to 10 patients, and a second multicentre study with 20 patients. Results seem to have been disappointing, with the mild initial improvements lost after 6 months.

Zrenner 2013 Has conducted a clinical trial with a microelectronic neuro-prosthetic device, powered via transdermal inductive transmission, carrying 1500 independent microphotodiode-amplifier-electrode elements (alpha IMS). Differently to PRIMA this device has an active receiver unit that is implanted behind the ear. This unit is connected via cable with a stimulation unit containing the electrodes. Nine blind subjects were provided with the device. Eight subjects were able to perceive light perception using the implant and six patients had a measurable grating acuity. Three subjects were able to read letters spontaneously and one subject was able to read letters after training in an alternative force choice test.

4.4. Risks and Benefits

4.4.1 Procedural Risks

The primary risks are associated with the surgical implantation of the device; these risks are associated with all retinal surgeries. Pixium Vision's PRIMA system and the corresponding surgical method have undergone risk analysis in accordance with EN ISO 14971:2009, IEC 60601-1 3rd, EN 60601-1-6:2010 and EN 62366:2008.

The following risks to the patient or tier user were identified during the risk analysis, were found to be acceptable and patient consent form as potential risks.

Risks related specifically to the PRIMA System:

- *Accidents due to temporary loss of visual perception*
- *Accidents due to unexpected non-function of the implant,*
- *Allergenic reaction*
- *Complications due to device explantation*
- *Impairment of residual visual function*
- *Damaged retina*
- *Dermal burns*
- *Electrical shocks from mains power supply*
- *Epileptic seizure*
- *Injury due to use of damaged external device or connection to/interfering with other devices*
- *Injury due to contact from external components*
- *Injury due to battery leakage, fire, or explosion*
- *Meaningful reduction of pre-implant visual function*
- *Minor electrical shock*
- *No increase of visual perception*
- *Retinal or Iris damage of a tier user (patient's family, etc.) or intended user due to exposure of infrared light of damaged external components*
- *Severe or non-severe tissue necrosis*
- *Skin burns to the physician, patient and/or tier user*
- *Strangulation with external components or asphysxiation*
- *Treatment delay*

Common risks from sub-retinal surgery:

- *Adverse reactions and risks to general/local anaesthesia*
- *Choroidal damage*
- *Chronic Hypotony leading to choroidal detachment or other complications*
- *Cell proliferation*
- *Corneal ulcer, damage to iris/crystalline lens*
- *Damaged retina*
- *Endophthalmitis*
- *Hanging eye lid/damaged eye muscle/damaged orbita*
- *Hypertony*
- *Infection*

- *Long term Hypotony*
- *Opaque media after surgery*
- *Peri-procedural problems typical of any major invasive eye operation*
- *Prolonged or aborted surgical procedure*
- *Retina detachment*
- *Severe non-treatable or non-severe retinal detachment*
- *Severe or non-severe intraocular inflammation/irritation*
- *Sympathetic ophthalmia*
- *Systemic or local poisoning*
- *Vitreous haemorrhage*

Pixium Vision has taken several measures to minimize patient risk. Only qualified trial investigators trained in vitroretinal surgery will carry out surgeries. Additionally, Pixium Vision will provide training to all study investigators with regard to the surgical methods prior to the first implantation.

The patients participating in the study are severely visually impaired on the study eye. The eye with the worst visual acuity is planned to be treated. Since most of the surgical risks are related to the eye only, the principle risk for the patient is damaging the remaining vision on the implanted eye. While, it is conceivable that more permanent damage, for example loss of an eye, could occur the data from pre-clinical studies would suggest that this is unlikely.

4.4.2 **Device-related Risks**

In addition to the above surgical risks the patient is made aware that additional sources of risk are psychological stress. As with any new experimental device there is a risk that the intended benefits are not achieved. A realistic risk for the patient derives from the disappointment if the device fails to meet the patient's expectations or worse still, if the device meets or exceeds the expectations of the patient but then stopped to work or need to be explanted due to complications. This can induce psychological stress and in the worst cases, depression for the patient. It is extremely important that all patients are aware of the risks and maintain realistic expectations of the experimental device. Every effort is therefore made at the time of recruitment and throughout the study to manage the patient's expectations.

Pixium Vision has developed their retinal prosthesis with requisite consideration to stimulation safety, material biocompatibility, surgical implantation methods, as well as safety requirements. During the development process, animal studies were conducted in order to mitigate risk.

4.4.3 **Benefits**

The investigational device has not been tested in humans before. Therefore, the benefit for blind patients is unknown. Animal tests suggest that the device will provide visual perception and therefore it is possible that patients may recognize and localize light sources, and recognize shapes of objects with high contrast, and potentially even recognize letters.

In summary, the devices tested in this study can potentially improve vision of the patient in a visual field area that previously could not provide vision.

4.4.4 **Risk/Benefit Assessment**

Patients selected for inclusion in the trial are carefully screened based on the study's inclusion/exclusion criteria. All patients are duly provided detailed and candid information concerning investigation and study procedures, as well as potential risks and benefits. In order to participate in the study, all subjects must review and, if in agreement, sign the Informed Consent document.

For this study only patients with severe vision loss on the study eye are included. To minimize the risks for the patient, patients with remaining useful vision on the non-study eye are selected. For those patients, the risk of losing a significant part of their sight is relatively low, since they still have useful vision on the non-study eye.

The potential benefits of restoring some level of useable vision for the patient are not inconsequential, and therefore, the benefits outweigh the risks.

Today patients with advanced dry stage AMD, visual re-education with low vision magnifiers has been the mainstay of treatment [http://www.amd.org/low-vision-rehabilitation]. Currently there are many nonsurgical options for visual re-education, some examples are: hand/stand magnifiers, spectacles, hand held telescopes, high plus spectacles in conjunction with high minus contact lenses to create a telescopic effect. Although these tools maybe effective for correcting overall visual functioning, there are several limitations especially when correcting distance and near acuity. In addition to the nonsurgical options there is currently one CE and FDA approved intraocular medical device based on the same concept of magnifier for retinal image enlargement. This intraocular telescope IMT manufactured by the company VisionCare is surgically implanted in the capsula bag and is held in position by haptic loop [Boyer 2015].

The PRIMA system with its very small size and its mechanism of action is not expected to yield the typical adverse events or limitations associated with intraocular telescope implantation such as:

- The size difference in the retinal images in the central field are too great to fuse binocularly.
- Non-corresponding images in the two eyes produce either double vision or binocular rivalry and suppression effects whenever both eyes are open.
- The differences in image size, motion, and brightness in the two eyes can promote diplopia by disrupting the normal neural mechanisms and feedback circuits that control binocular eye position and movements.
- The binocular temporal field is obstructed on the side of the intraocular telescope-implanted eye,
- When the intraocular telescope field suppresses the overlapping region of the fellow eye field, vision is obstructed in the annular region of the binocular visual field between the unmagnified and magnified outer limit of the intraocular telescope field,
- Retinal illuminance in the intraocular telescope implanted eye will be reduced by attenuation factors about 0.8 and 1.0 log units, comparable to wearing a monocular sunglass and impacting both contrast sensitivity and acuity in dim light conditions in the intraocular telescope implanted eye.

A risk management process compliant with EN ISO 14971:2012 identified appropriate risk control measures and confirmed that the risks to patients from the use of the PRIMA system have been reduced in line with the standard of care. It is concluded that the residual risks associated with the use of the PRIMA system, when used in accordance with the Instructions for Use are acceptable.

4.5. Surgical training

All surgeons implanting the PRIMA must participate in surgical training procedure. The procedure includes a presentation of the surgical method according the Instructions for Use, a presentation of the surgical method by an experienced surgeon, and a minimum of 5 in vivo implantations in animals or equivalent.

4.6. Route of Administration, Treatment Periods

4.6.1 Route of Administration

The device will be implanted as stated in the instructions for use. For details see also section 8.1.5.

4.6.2 Treatment Periods

Appendix A contains a schedule of study related treatments and evaluations.

4.7. Statement of Compliance

- Sponsor and Investigator will conduct the study in accordance with the ethical principles outlined in the Declaration of Helsinki (latest version);
- Sponsor and Investigator will comply with ISO 14155:2011 and any regional or national regulations;
- Investigator will not begin until the study obtains the required written approval or favourable opinion from the Ethic Committee or regulatory authority;
- Investigator will follow any additional requirements imposed by the Ethic Committee or regulatory authority;
- Sponsor will provide insurance for subjects.

4.8. Description of Subject Population

The device in the present investigation is indicated for subjects suffering from dry macular degeneration. All eligible subjects will be screened for inclusion in the study. All Subject exclusions will be documented on the screening log.

4.9. Scientific Background, References in Literature

Appendix E contains a list of references.

5. Trial Objectives and Purpose

This investigation is an open-label, prospective, non-randomized, multicentre, first in human clinical trial. The objective of this study is to evaluate the safety and performance of the PRIMA System in patients with dry macular degeneration.

In addition to the safety evaluation this feasibility study is used to demonstrate the basic functionality of the device in subjects with dry macular degeneration. This data is necessary for further development of the device towards a long-term treatment for dry macular degeneration. This data cannot be generated by animal trials since the retinae of the animal model is different from patient with dry macular degeneration and animals cannot describe precisely what they see.

6. Trial Design

6.1. Specific Statements of Primary and Secondary Endpoints

The primary efficacy endpoint is the assessment of the device performance to demonstrate principal functionality of the PRIMA system. It is assessed by measuring the capability of the patient to perceive light at specific locations. To prove the functionality of the device, patients are tested with the device on and off. At 6 weeks, 3, 6, 12, 18, 24, and 36 months after implantation. In this feasibility study the fundamental function of the PRIMA device will be tested by OCTOPUS visual field measurement.
The visual acuity will be measured with the Landolt test as a secondary endpoint for all subjects once it is approved. The first time this new test is measured depends on the follow-up time point the subject is approaching and will be the earliest after 18 months follow-up. Afterwards the Landolt C test will be measured at 24 and 36m.

The primary safety endpoint of the study will involve an analysis of the incidence, severity and duration of all adverse events at 1 day, 1 week, 1, 1.5, 3, 6, 12, 18, 24, and 36 months**.** The safety of the implanted device will be assessed in a series of regular ophthalmologic examinations designed to capture any pathological changes in the eye as a result of device implantation.

All adverse events according to section 10 will be recorded. Every adverse event will be identified by a name defined by the investigator (e.g. retinal detachment). During later analyses of the safety the “incidence” of every adverse event will be compared to adverse event rates of other comparable devices which are already on the market for similar indications (e.g. ARGUS II, Second Sight Medical Products, USA). The investigator rates the “severity” of an adverse event by rating it as mild, moderate or severe. He/she also check if the criteria for serious adverse events according to Section 10 are fulfilled. The investigator also rates the likelihood of adverse events being device related or procedure related by choosing the appropriate term defined in Section 10. All adverse events are followed until they are solved or medically stable. Medically stable events are events that are not expected to be completely resolved but reached a status where no further treatment or treatment change will be necessary. The “duration” of an adverse event is defined as the time between date of onset and the date when the event is resolved or medically stable status has been reached.

All device or procedure related adverse events and all serious adverse events are reviewed by a clinical event committee (CEC) consisting of at least two independent ophthalmic specialists with an extensive experience in the field of ophthalmology. The CEC members have experience in vitreoretinal surgeries, know possible side effect of

such surgeries. The CEC members serve in an individual way and provide their expertise and recommendations. The CEC members are notified of an adverse event requiring adjudication and receive all required information needed for the event adjudication (e.g. report of intervention, imaging data if applicable). The event is considered final if majority agreement of adjudication is obtained. If no majority is obtained the event is discussed during a call to achieve final adjudication.

Visual outcome tests are defined in more details in Appendix C.

6.2. Type and Design of Trial, Procedures and Stages

The study is an open-label, prospective, non-randomized, multi-centre, first in human study occurring at several investigational sites.

In this study, up to five subjects can be enrolled. In a first phase, three subjects will be enrolled and implanted. The study will be interrupted if none of the implanted subjects had visual perception elicited by the implant and/or an unacceptable device or procedure related adverse event occurred.

After an initial evaluative and training period, in which subjects will learn to use the device within a controlled laboratory environment, subjects will be allowed to take the device home and utilize it in their own environments for performance of specific tasks linked to the study objectives.

Procedures include:

1. Patient recruitment and Screening
2. Informed consent
3. Pre-Surgical ophthalmological examination
4. Baseline Vision testing
5. Implantation
6. Follow-up Assessments post-implantation
7. Silicone oil removal (if silicon oil was used)
8. Follow-up Assessments, stimulation assessments and home use

See Appendix A for a detailed schedule of procedures.

6.3. Measurements to Minimize Bias (including randomization + blinding)

The trial is an open-label, non-randomized, multicentre, prospective, first in human trial. Please see Statistical Section 11.

6.4. Trial Treatment, Product Packaging, Labelling

All treated subjects will receive a PRIMA System manufactured by Pixium Vision. The device consists of an implantable Retinal Implant, as well as a non-implanted Visual Processor.

The Retinal Implant is packaged in a sterile container together with a delivery system and labelled with the following information:

PRIMA Retinal Implant
Pixium Vision SA, 74 rue du Faubourg Saint Antoine, 75012 Paris, France
Exclusively for clinical investigations
Product reference
Serial number
Sterile/EO
Sterility expiration date
Single-use device.

The Visual Processor is labelled with the following:
PRIMA Visual Processor
Pixium Vision SA, 74 rue du Faubourg Saint Antoine, 75012 Paris, France
Exclusively for clinical investigations Serial number
Product reference

The serial numbers for each component will be documented in the respective CRFs.

6.5. Subject Participation

The subject is enrolled from the moment the subject signs and dates the patient informed consent form. The site will inform the sponsor about the enrolment of a patient immediately after he or she signed the informed consent. The sponsor keeps a log of enrolled patients and informs the sites as soon as the maximum number of subject is reached.

All subjects consented to participate in the trial are expected to complete the study throughout 36 months of follow-up. After the trial treatment of 36 month has been finished participants are asked to visit the hospital at minimum every 2 years as long as the implant is in the eye. For subjects that have finished the study the participating sites are asked to examine the subjects per standard of care and to report all device or procedure related adverse events to Pixium Vison.

Appendix A describes the schedule of procedure and follow up assessments.

6.6. Trial Stopping Rules and Discontinuation Criteria

The Sponsor or Principal Investigator may terminate the study at any point if:

- Permission for the study is revoked by a regulatory institution;
- A serious or unanticipated adverse event occurs which presents unacceptable risk for patients.[1]

An individual may terminate their participation in the study at any point. It is recommended that the subject should discuss withdrawal from the study with their physician to ensure that withdrawal is managed in such a way as not to increase patient risk.

The trial will be interrupted if after implantation and activation of the first three subjects none of the subjects had visual perception evoked by the investigational device. In this case data will be reviewed and changes in the procedures and/or medical device may be required. If at least one of the first three subjects has perception elicited by the implant the study continues as planned with up to five subjects.

6.7. Accountability Procedures

A log of all implants and patients will be maintained. No implant will be stored at the clinical sites. Any explanted devices will be immediately returned to the sponsor.

6.8. Identification for Direct CRF Data Considered as Source Data

All investigators will be required to maintain study worksheets for ophthalmological and functional assessments, as well as clinical dictations, which may serve as source

[1] Pixium Vision continuously update the risk analysis for PRIMA. The risk analysis is performed according ISO EN 14971:2012. The data for severity and likelihood of individual adverse events are fed into the risk analysis. If this leads to one or more unacceptable risks, and no measure can be introduced to reduce the risks the complete study then, in compliance with ISO EN 14971:2012, the study will be stopped.

documentation. No information should be transferred to a CRF that does not have a corresponding source at the clinical site. See Appendix D.

6.9. Participating clinical sites

The trial is designed as a multi-centre trial and the sponsor keeps a list of all participating clinical sites. Since the study uses competitive patient recruitment it is possible that all patients are enrolled in one site.

7. Selection and Withdrawal of Patients

Patients will be assessed for inclusion in the study based on the criteria outlined below. If patients meet the inclusion criteria, they will be invited to participate in the study. After signing the Informed Consent, a detailed study ophthalmological exam will occur in order to verify all Inclusion/Exclusion criteria. If any patients fail to meet Inclusion/Exclusion criteria after the complete study pre-surgical ophthalmological exam, he/she will be withdrawn from the study and considered a screening failure. Once patients meet all Inclusion/Exclusion criteria they will be implanted with the device.

7.1. Patient Inclusion Criteria

Patients will be included in the study provided that he or she:

- Is 60 years or older at the date of enrolment;
- Has a confirmed diagnosis of advanced dry age related macular degeneration with an atrophy size of at least 3 optic disc diameters;
- Has best corrected visual acuity of the study eye of logMAR 1.3 (20/400) or worse measured by ETDRS;
- Has no foveal perception measured by micro-perimetry in the study eye (≤ 4 dB on Opko scale or equivalent)[2];
- Has a study eye that is able to perceive light;
- Has useful vision on the non-study eye;
- Has a refraction of study eye between –3 and + 4 (limits included) for patient with IOL (there is no refraction criteria for patients with natural lens);
- Understands and accepts the obligation to present for all schedule follow-up visits.
- Patient signed informed consent

[2] Please see protocol appendix G for a detailed microperimetry protocol

7.2. Patient Exclusion Criteria

Patients will be excluded from the study if he or she:

- Has cataracts that may influence the visual function of the study eye;
- Has an aphakic study eye
- Had cataract surgery in the last 1 month;
- Active sub-macular choroidal neovascularization in the study eye;
- Has any disease (other than study allowed diseases) or condition that affects retinal function of the study eye (e.g., central retinal artery/vein occlusion, end-stage diabetic retinopathy, retinal detachment, infectious or inflammatory retinal disease, severe glaucoma, optic neuropathy, myopic chorio-retinal atrophy etc.);
- Has an implanted telescope in one eye;
- Has any disease or condition that prevents adequate examination of the study eye including, but not limited to, corneal degeneration that cannot be resolved prior to implantation. Note, that this criterion is also important for the function of the implant;
- Has an endothelia cell count of less than 1000 cells/mm² in the study eye;
- Suffers from nystagmus;
- Has any disease or condition that precludes the understanding or communication of the informed consent, study requirements or test protocols (e.g., deafness, severe multiple sclerosis, amyotrophic lateral sclerosis, severe neuritis, etc);
- Has a history of epileptic seizure;
- Has a history of chronic or recurrent infection or inflammation that would preclude participation in the study;
- Has a known sensitivity to the contact materials of the implant (iridium oxide, silicon-carbide and titanium);
- Presents with hypotony in the study eye;
- Presents with hypertony in the study eye;
- Has another active implanted device (e.g. cochlear implant, pacemaker) that may interfere with the device function, or diagnoses requiring such an active implant;
- Has active cancer or a history of intraocular, optic nerve or brain cancer and metastasis;
- Is an immune-suppressed subject (e.g., due to HIV positive diagnosis, etc.);
- Is carrier of multi-resistant germs;
- Is receiving anticoagulation therapy that cannot be adapted to allow eye surgery;
- Is participating in another investigational drug or device study that may interfere with the present study;
- Patients with recurrent or chronic inflammations or infections are excluded from the study. Specifically, patients with the following disorders are excluded:

  - Common inflammation – severe chronic and consuming diseases that frequently associated with infection (e.g. Crohn disease, Whipple's disease);
  - Active inflammation in the area of the eye (e.g. herpes of cornea and/or conjunctiva, recurrent blepharoconjunctivitis, horedolum, chalazion);
- Has a severe psychological disorder. When in any doubt, an expert assessment needs to be arranged to clarify whether the patient's psychological health is suitable for the trial. In any doubts of the subjects psychological status a clinical psychologist, psychologist or the community doctor/general practitioner should be involved. The patient must have the legal capacity to sign the informed consent;
- Has severe renal, cardiac, hepatic etc. organ diseases;
- Has head dimension that are incompatible with the Visual Interface.
- Has too high and unrealistic expectation (e.g., believes that a benefit is guaranteed or expect normal vision after surgery);

7.3. Criteria and Procedure Specifications for Subject Withdrawal

Patients may withdraw their consent for participation in the investigation at any time.

Patients may also be withdrawn from the study if:

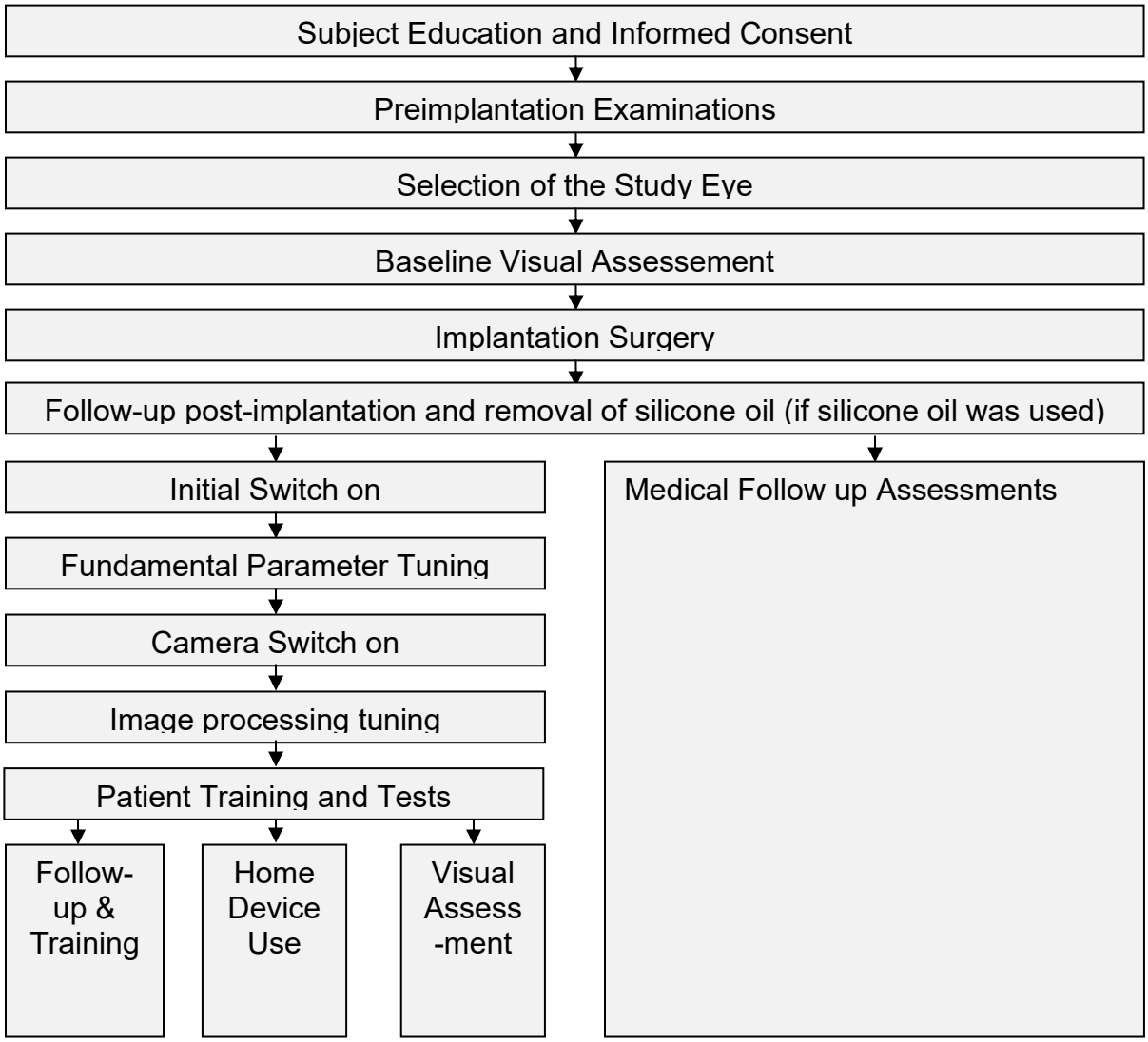
- He or she significantly fails to comply with the study follow-up schedule;
- In the opinion of the treating investigator continuation in the study jeopardizes the subject's health and/or well-being;
- There are significant protocol violations surrounding the patient's original inclusion in the study;
- Either the Sponsor or a governing regulatory authority discontinues the study.

8. Treatment Plan and Follow-Up Periods

8.1. Treatment Plan

Patients will be followed for 36 months post implantation. As part of follow-up, all subjects will be required to undergo ophthalmologic examination, testing, and/or training. Appendix A contains the master schedule of events occurring at each follow up visit. Several sessions may be required per follow-up period to complete all scheduled tasks. Appendices C contains sub protocols with specific instructions for each of the assessments. A summary of procedures and assessments is found over-page followed by a listing of study follow up intervals. In addition to the follow up visits listed in Appendix A, training and tuning sessions will take place.

The investigational plan is structured as follows:



8.1.1 **Subject Education and Informed Consent**

The clinical investigator informs the patient of his/her rights and obligations and that the retinal implant is an investigational device. If the subject agrees to participate in the study, a signed informed consent will be obtained prior to the pre-surgical examination.

The informed consent must be read to the subject by a member of the study team. A witness must be present during the informed consent procedure who confirm that the blind subject had been consented. The witness is ideally a family member or a friend of the subject. If no family member or friend of the subject is available the witness can also be an employer of the study site or other person but must be independent from the study (e.g. it cannot be the investigator).

8.1.2 **Pre-implantation Examination**

Before implantation of the device the examinations in accordance with Table 1 are performed on both eyes.

Table 1: Ophthalmological examination (*is only done pre-implantation)

Examination	Description
Medical history*	Information related to the patient's past medical history, medications, demographic information, and disease state will be recorded
ETDRS	Visual acuity measured by ETDRS standard (without device)
Microperimetry	A microperimetry (e.g. Optos) will be used to measure visual field loss (see Appendix G for a detailed protocol)
Objective refraction	The objective refraction should be measured 5 times at each eye. The values for the median sphere are used for each eye
Slit-lamp	The subject anterior segment of the eye is examined with a slit-lamp
Funduscopy	The posterior part of the eye is examined with a slit lamp. The macular and the peripheral retina is assessed separately
Fundus photography	A colour image of the retina is done with the macular centred (50º or 60º). Wide angle photography is preferred)
Indocyanine angiography (ICG)	ICG images are performed with the macula centred (wide angle photography if preferred if available this is preferred, i.e. OPTOS wide angle ICG)
Fluorescein Angiography	Fluorescein Angiography images are performed with the macula centered. Wide angle photography is preferred if available, e.g. OPTOS wide angle FFA)
Autofluorescence imaging	Autofluorescence imaging is performed and the atrophy size is measured manually of semi-automatically.
Optical Coherence Tomography (OCT)	The area of the implant is scanned to identify the distance between electrodes and retina e.g. with a cube measurement. The preferred device is SPECTRALIS (Heidelberg Engineering, Germany). Before implantation the area of the macula is scanned. The measurement should be done 3 times to see influences of possible eye movements. In addition to the implant region the peripheral retina is also examined (see Appendix G for a detailed protocol)
Tonometry	Intra ocular eye pressure is measured

Endothelial cell count*	Endothelial cells of the cornea are counted[3]
OCTOPUS Visual Field	See endpoint test in Appendix C.
Binocular visual field	A binocular visual field is measured (e.g. Estermann)
Visual acuity	Measured with Landolt C see Appendix C3

8.1.3 **Selection of the Study Eye**

The eye with the lesser visual function will be selected.

8.1.4 **Baseline Visual Assessment**

All patients will be assessed for all visual function tests thereby providing baseline data for comparative purposes. The fellow eye is measured as a control.

8.1.5 **Implantation Surgery**

The implant procedure is performed following the procedure in the instruction for use.

The investigator will discuss with the responsible anaesthetist and the patient whether the surgery will be undertaken under local or general anaesthesia.

For patients with a natural lens the lens will be removed during the implantation surgery. The natural lens must be removed by phako-emulsification and a hydrophobic acrylic IOL (e.g. 12.5 mm Alcon UltraSert) monofocal lens is implanted). These IOLs have CE mark and are standard in cataract surgery.

For patients with an artificial IOL, the artificial IOL will be left in place.

The PRIMA device will be implanted in the foveal region where there is no perception measured before implantation. The implantation procedure of PRIMA implant chip is done per the following procedure:

Step	Operation
1	Open conjunctiva in lateral canthal area, leaving an anterior flap of 3 mm.
2	Sclera cautery in the ports area.
3	Set 23Ga ports for vitrectomy (3 to 4mm from limbus)

[3] Endothelia cell count is done before the implantation to give the investigator more information about the risk of corneal decompensation. Which could lead to exclusion of the subjection if it is detected before implantation. After implantation endothelia cell count is not done since the occurrence of corneal compensation would be detected by slit lamp examination.

Step	Operation
	• Place Infusion at lateral canthal area. • Place working ports narrowly so there is full exposure but adequately comfortable for the surgeon. • Place chandelier to allow two-hand manipulation.
4	Perform a complete vitrectomy.
5	Prepare syringe with BSS and subretinal cannula to create retina bleb (e.g. 25 Ga cannulas with 38 to 41 Ga tip). Recommended: connect BSS syringe to silicone oil injection system.
6	Introduce cannula into the eye and make sure there are no air bubbles in the cannula.
7	With max 20psi pressure, slowly inject BSS subretinally between the macula and the upper retina vessels to create a bleb in the upper temporal part of the posterior pole. It is recommended to start injecting BSS before introducing the tip of the cannula below the retina. Warning: the fovea is a fragile area that may perforate in this operation, proceed carefully.
8	If necessary, smoothly massage the bleb to correct its position by using a smooth tip backflush and air-water exchange. Make another bleb if the macula is not lifted.
9	Make retinotomy with vertical scissors. Position: near or between the upper retina vessels, 4 to 5mm from the fovea. Length: 2 to 2.5 mm, as determined relatively to the optic disc size pre-operatively. Avoid the preferred retinal location for the retinotomy. In case of high risk of bleeding, endodiathermy can be used within this zone.
10	Coagulate sclera incision for implant insertion (3 to 4mm from limbus, centered in the temporal superior quadrant in alignment with the retinotomy).
11	Make 2.0 mm incision with 2.0 mm knife at 3 to 4mm from limbus. If necessary, cauterize choroid behind sclerotomy using endodiathermy and clean incision with vitreotom to remove remaining vitreous for sharper choroid cut at sclerotomy location.
12	Preplace a suture on the sclerotomy for temporary closing to limit leakage (recommended Vicryl 6-0, alternative Vicryl 7-0).
13	Assistant: prepare a backflush with a syringe of PFC (e.g. DK-Line from Bausch and Lomb or Deca from FCI)
14	Introduce the backflush connected to a syringe of PFC in the eye.
15	Prepare for two-hand manipulation: backflush + PRIMA Delivery System with plastic holder removed.

Step	Operation
16	Introduce the implant with the Delivery System straight into the eye without turning the implant in the sclera incision. Disable infusion until the sclerotome suture is pulled.
17	Assistant: pull the sclerotomy suture to reduce fluid leakage through the sclerotomy.
18	Before releasing the implant, make sure there are no turbulences in the eye: implant sclerotomy is tighten, trocars are tight, infusion pressure is low, pressure compensation is deactivated.
19	Introduce the implant in the subretinal space. Release it smoothly, and position it under the fovea by pushing it with the soft tip of the backflush or another appropriate instrument if necessary.
20	Immediately inject PFC with the backflush, fill to equator level beyond the retinotomy.
21	Disable infusion while removing the Delivery System from the eye. Close the sclerotomy.
22	Optional: Image the retina with OCT to confirm absence of liquid under the retina. If liquid remains, it needs to be removed.
23	Perform a fluid/air exchange removing PFC and remaining subretinal liquid with the backflush.
24	In case of high risk of retinal detachment or implant migration an appropriate tamponade should be used (for example 25% SF6 gas or silicone oil, FCI 1000cs).
25	Close sclerotomies and entry ports, recommended: Vicryl 8-0 or 7-0. If necessary replace vicryl 6-0 by vicryl 8-0 or 7-0. Verify that the eye is tight.
26	Suture conjunctiva, recommended: Vicryl 8-0 or 7-0.
27	The patient should be stabilized for minimum of one hour immediately after surgery.

The duration of the surgery is planned to be between 1 and 2 hours.

At least one Pixium employee will be present for each implantation procedures to provide the implants and to assist with technical advice.

Post-implantation the patient will be examined per examination listed in Appendix A and hospital standard of care after intraocular surgeries.

Approximately four weeks after implantation the silicone oil that may have been used during implantation surgery will be removed by the surgeon. Removal of silicone oil is a

standard process in ophthalmology. The silicone oil will be replaced by a sterile salt solution.

8.1.6 **Post-Surgical Follow-Up Ophthalmologic Assessments**

Implantation is followed by the examinations listed in Table 1 at time intervals defined in Appendix A to confirm healing, assess patient outcomes and to observe the presence of any complications. Both eyes are examined.

If the patient undergoes surgical or therapeutic (e.g. MRI) intervention, the patient must undergo an ophthalmological examination prior to continuing with the study and the use of the device.

8.1.7 **Tuning and Training Sessions**

After implantation, a series of visits is planned to tune the parameters of the implant and train the patients to use the device. Tuning and training is done according to Pixium Vision's standard operating procedures. Trained clinical personnel will perform these sessions. A Pixium Vision employee or designee may be present during these sessions.

Prior to the first activation of the implant the subject will be trained to control their eye movement. They will be asked to look into specific directions by guiding the hands of the subject in front of the head and asking the subject to concentrate on their index finger even if they are not able to see it. This training will also be done in conditions where it is not possible to see the index finger, e.g. the therapist hold a piece of paper between the hand and the eyes. This exercise may be very important because the gaze need to be aligned with the infrared beam of the device to target the implant in the eye.

The first activation of the implant is termed "Initial switch-on". This occurs approximately one week after silicone oil removal or three weeks after implantation. Note that in the first sessions the camera will not be used. The activation of the implant will be driven by a connected computer and the stimulation will not depend on the environment in front of the camera. During the initial switch on session, first the glasses are mechanically fitted to the dimension of the subject head. Specifically, the position and possibly the shape of the nose pad is adjusted. In addition, the position of the projection system is adapted. Both nose pad position and projection system position ensure that the projector is in front of the subject's pupil and the projected IR light pattern reaches the implanted chip. Nevertheless, it is made sure that the Visual Processor is comfortable to wear.

As a next step, the subject will be asked to hold the gaze straight forward, the implant system will be activated and short pulses with large spot size will be executed. The subject will be asked about perception. If the subject reports about perception a verification will be performed. In this verification stimulation will be mixed with non-stimulation. The subject will be asked to differentiate between stimulation and non-stimulation to verify the reliability of the subject perception. If this does not create verifiable perception the subject will be asked to look into other specific directions and the stimulation test is repeated. In this way, the application of IR projection will be done at different location on the retina to identify the gaze that is needed to target the implant. Note that nominal gaze should be straight forward but a slight misalignment of the visual processor could lead to a non-function of the implant. As soon as a location is identified that created perception when the implant is activated by IR light the position of the glasses may be adjusted.

After principle function of the implant has been shown and the connection between IR projector and implant is established, basic parameters of the stimulation will be evaluated. Therefore, the pulse duration and the intensity of the stimulus will be varied and the subject will be asked about perception. Pulse duration will be varied between 0 and 9.8 ms. IR intensity will be varied between 0 and 3 mW/mm^2. In this way parameters will be identified that maximize the likelihood of perception. These parameters will be set for the following use of the camera.

After the principle parameters of the device are tuned the camera will be activated. From that moment, the activation of the implant will depend on the environment in front of the subject. In the following sessions, the subject need to learn to use the new kind of vision. Therefore, visual task will be trained using the principles of visual reeducation. The first task will be very simple e.g. to detect a white paper on black background. It will follow the localization of a white object on a black background. All the time the subject will be reminded to hold the gaze in the prior identified direction. More difficult tasks will be to identify the orientation of an object or to discriminate the size and shape of objects. In a more advance stage of the training the contrast and color of the objects will be varied. The training program will vary in intensity and speed depending on the mental capability and visual outcome of the subject. Since this is the first time the investigational device will be used it is expected that also the tuning and training program need to be adapted during the treatment.

8.1.8 **Home Device Use**

After tuning and training, patients may be permitted to use the device at home and in non-clinical environment for performance of specific tasks linked to the study objectives. A home use record will be completed and provided to Pixium Vision. The device can also be used after the end of the clinical trial if beneficial for the patient.

The system logs user interaction (pressing of user buttons) and possible error messages during tuning and training sessions and also during home use in an internal memory. These logfiles will be read out by clinical staff and sent in anonymised form to Pixium Vision

8.1.9 **Additional Tests**

At the discretion of the investigator, additional tests may be performed. The purpose of these tests may include verifying the system function, to gather data, to develop additional tests, and/or to obtain information that will not otherwise be gathered by the prescribed tests detailed in Appendix C. Focus of additional tests will be e.g. daily living activities and central visual function. Certain tests may be developed during the study.

8.1.10 **Use of Medications**

Permitted Medication

Any drugs administered are considered collateral drugs. All collateral medications will be recorded on subject case report forms.

Non-permitted Medication

Anticoagulation therapies need to be adapted to the surgical procedure. This will depend on the specific drug the individual subject uses.

8.1.11 **Psychological care**

In the event that the expectations of the patients are not met, there is a need for provision of psychological care. In this case the psychological service (e.g. the clinical psychologist of the hospital) will be used for the patients care together with the responsible investigator. In addition, psychological care can be requested by the patient at any time during the study.

8.1.12 **Explantation**

Explantation of the device will only take place to resolve significant adverse events or in case of early device failure. In case of a planned explantation the risk and benefit of the procedure should be carefully evaluated in light of the individual conditions of the patient eye.

If the implant failed to work within the 36 months study follow up because of a deterioration of the implant that leads to a nonfunctional device, it will be explanted, except the individual condition of the subject's eye does not allow a safe explantation. The explanted device will be brought back to Pixium Vision for a detailed analysis of the implant failure.

In the absence of significant adverse events or device failures, the device remains implanted after study subject participation ends. The physician will follow up with the patient per hospital standard of care, and no study data will be collected after the subject exited the study.

If an explantation will be necessary because of medical issues or an early device failure, the procedure will be done in the same manner as the implantation but instead of introducing the implant in the sub retinal space the implant will be removed.

8.2. Follow-Up Intervals

Appendix A contains a schedule of procedures and tests to be accomplished at given time points after implantation. If wound healing is not completed after four weeks the whole assessment schedule is delayed by the extra period required for healing.

8.3. Subject follow-up after study exit

All subjects consented to participate in the trial are expected to complete the study throughout 36 months of follow-up. After the trial treatment of 36 months has been finished participants are asked to visit the hospital at minimum every 2 years as long as the implant is in the eye. For subjects that have finished the study the participating sites are asked to examine the subjects per standard of care and to report all device or procedure related adverse events to Pixium Vison.

9. Assessment of Performance

This section describes the procedure to measure the performance endpoints of the device.

The performance endpoints of this study are defined in terms of elicitation of visual perception. In this feasibility study the performance of the device will be measured using OCTOPUS visual field measurement. The function of the device is demonstrated by measuring the subject's capability to carry out tasks with the device "on" compared to the

device switched off (wearing the visual interface). In addition, the visual field is measured at baseline and without the device at each follow-up interval according Appendix A.
In addition to Octopus, the visual acuity will be measured according to Appendix C3.

The performance endpoint is measured at a number of time points throughout the study. All endpoint testing will be conducted under the supervision of qualified Health Care Professionals.

Appendix A contains a listing of stimulation sessions at various time points throughout the study. Appendix C contains the end point testing procedures.

10. Assessment of Safety

10.1. Specification of Safety Parameters

The safety of the implanted device is assessed by regular ophthalmologic examinations to assess pathological changes within the eye and retina (see Table 1). Additionally, stimulation thresholds are observed. Please refer to Appendix A for a schedule of events dictating patient follow-up.

Events will be assessed by an independent Clinical Event Committee (CEC). All serious adverse events, all device related and procedure related adverse events will be adjudicated by the CEC members.

10.2. Procedures for Reporting and Recording Adverse Events

Subjects will be carefully monitored during the study for possible Adverse Events (AEs) from the time the subject signs the Patient Informed Consent form to the completion of their participation in the study. Any AE observed will be fully investigated by the Investigator and classified in line with the definitions of the ISO14155:2011, which are shown below.

10.2.1 **Definition: “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.

This definition includes events related to the investigational medical device or the comparator. This definition includes events related to the procedures involved. For users

or other persons, this definition is restricted to events related to investigational medical devices.

All adverse events must be documented on patient Case Report Forms. An adverse event can be characterized as serious (SAE). A serious adverse event can be characterized as an unanticipated adverse event (UAE).

10.2.2 **Definition of "Serious Adverse Event" (SAE)**

A serious adverse event is defined as an event that

a) led to death;
b) led to a serious deterioration in the health of the subject, that either resulted in
   1) a life-threatening illness or injury, or
   2) a permanent impairment of a body structure or a body function, or
   3) in-patient hospitalization or prolongation of existing hospitalization, or
   4) in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function;
c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

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.

10.2.3 **Definition of "Adverse Device Effect" (ADE)**

Adverse event related to the use of an investigational medical device.

This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

10.2.4 **Definition of "Serious Adverse Device Effect" (SADE)**

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

10.2.5 **Definition of "Unanticipated Adverse Device Effect" (UADE)**

Any adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously

identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

An Unanticipated Serious Adverse Device Effect (USADE) occurs when an event's nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

An anticipated Serious Adverse Device Effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

10.2.6 **Definition of "Device deficiency"**

Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error or inadequacy in the information supplied by the manufacturer.

10.2.7 **Definition of "Use error"**

Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

Use error includes slips, lapses, and mistakes. An unexpected physiological response of the subject does not in itself constitute a use error.

10.2.8 **Event severity classification**

Mild: Awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolved without treatment and with no sequelae.
Moderate: Interferes with the patient's usual activity and/or requires symptomatic treatment
Severe: Symptom(s) causing severe discomfort and significant impact on the patient's usual activity and requires treatment

10.2.9 **Causality relationship**

The investigator will assess the causality of all adverse events in relation to the research, i.e., the relationship between the AE/SAE and the investigational treatment or any other study-related procedures.

Each SAE will be classified according to five different levels of causality:

1) **Not related**: relationship to the device or procedures can be excluded when:
   - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
   - the event has no temporal relationship with the use of the investigational device or the procedures;
   - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
   - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
   - the event involves a body-site or an organ not expected to be affected by the device or procedure;
   - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
   - harms to the subject are not clearly due to use error;
   - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2) **Unlikely**: The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3) **Possible:** The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4) **Probable:** The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.

5) **Definite/Causal relationship**: The serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
    - the investigational device or procedures are applied to;
    - the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

10.2.10 **Investigator Reporting Responsibilities**

10.2.10.1. Notification of events to the sponsor

The investigator should report to the sponsor the following events, whether expected or not, in the corresponding sheet of the CRF, with the exception of AEs/SAEs detected before the patients has signed the patient consent form.

- AE
- SAE
- Device Deficiencies that did not but might have led to a SAE if:
    - Suitable action had not been taken or
    - Intervention had not been made or
    - If circumstances had been less fortunate
- New findings/updated in relation to already reported events

If an AE/SAE is present at the beginning of study prior to the subject providing signed consent to participate in the study, only its worsening should be reported.

The investigator shall notify the sponsor immediately and not later than 24 hours after the investigator has become aware of a SAE or device deficiency that might have led to a SAE.

The investigator must ensure that all additional relevant information that becomes available is also forwarded to the sponsor immediately after the initial notification.

The investigator shall transmit to the sponsor all relevant supporting documents related to the SAE (i.e., copy of laboratory exams, hospitalization reports indicating the SAE) ensuring anonymization of the documents and indicating the identification number of the subject in the trial.

10.2.10.2. How to report

The investigator will report to the sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect.

All Serious Adverse Events (SA(D)Es), including all device deficiencies should be reported to the Sponsor within **24 hours** of awareness of an event via the Adverse Event Electronic Case Report Form in the study's electronic database, as that will trigger an immediate e-notification to the Sponsor and MedPass. Additional information can be provided to the Sponsor or MedPass via email, telephone, or fax using the information below.

Pixium Vision	**MedPass International SAS**
74, rue Faubourg Saint Antoine	95bis, Boulevard Pereire
75012 – Paris - France	75017 – Paris – France
Fax: +33 1 84 10 80 17	Fax: +33 1 40 53 81 11
Tel: +33760814022	Tel: +33 1 42 12 83 30

The investigator will document all AEs on the Adverse Event Form, including (at a minimum) a description of the event, date of onset, severity, relationship to the investigational device and/or procedure, required interventions, duration, and outcome.

The investigator will monitor all AEs until they are resolved, determined to be a chronic condition or the subject is lost to follow-up. The investigator will report all AEs regardless of whether it is anticipated or unanticipated and regardless of classification, seriousness, intensity, outcome or causality.

The clinical monitor will ensure that all adverse events have been detailed appropriately and fully documented on subject Case Report Forms.

10.2.11 Reporting to Ethic Committee / Competent Authority

Depending on the local requirements or following agreement between both parties, the sponsor or the principal investigator will be responsible for performing safety reporting to the Ethics Committee according to the relevant local regulatory requirements.

The sponsor will be responsible for reporting to the National Competent Authority according to national requirements and in line with MEDDEV 2.7/3 and/or MEDDEV 2.12-1, as applicable.

11. Synopsis of Statistical Approaches

11.1. Introduction and Study Populations

Plans for the specification and reporting of data analyses were developed in consideration of ICH guidelines E3 (Structure and Content of Clinical Study Reports, 1995), E9 (Statistical Principles for Clinical Trials, 1998), and other industry, statistical, and regulatory guidance; opinions regarding good clinical and good statistical practice; and where appropriate, substantive clinical experience.

All patients who meet the inclusion and exclusion criteria and receive a retinal implant will be considered part of the primary safety cohort.

11.2. Objectives

The primary objective of this study is to evaluate the safety and performance of the PRIMA System in patients presenting with dry macular degeneration.

Safety evaluations will involve summarizing the incidence, severity and duration of all adverse events. The safety of the implanted device will be assessed in a series of regular ophthalmologic examinations designed to capture any pathological changes in the eye as a result of device implantation.

Performance will be evaluated by OCTOPUS Visual Field measurement.

11.3. Sample Size Estimate and Justification

To assess the safety and performance of the PRIMA System initially a maximum of five implanted subjects is planned for this first in human study. This number is deemed sufficient to determine the extent to which the PRIMA system can evoke perception.

11.4. Analysis Methods

11.4.1 **Primary Analyses**

Before proceeding with the analysis of primary research questions, data will be fully described including aspects of data quality. Graphical methods like histograms, scatter plots, and box plots will be used in order to understand aspects of data quality and examine assumptions (such as normality) underlying statistical models. Plots of measured variables over time to assess patterns of change will be especially important for specific clinical endpoints to be collected longitudinally; both subject-specific values over time will be examined. Means, standard deviations, medians, and ranges will be computed for measured interval variables; marginal distributions will be used for categorical factors. The amount and patterns of missing data, if any, will also be characterized.

11.4.2 **Interim Analyses**

Interim analyses of the study will be performed after a minimum of three patients passed the six-month examination. The purpose of the interim report will be the preliminary conclusion about the performance and safety of the device to continue with further development and to initiate a pivotal clinical trial.

11.4.3 **Accounting missing, unused or spurious data**

No replacement of missing data will be performed in the statistical evaluation of results.

12. Monitoring / Direct Access to Source Data

The subject will agree to study procedures and the accessibility of the data through the informed consent process.

The trial investigator will guarantee the sponsor, monitor, and regulatory authorities direct access to relevant subject medical charts and other study documents to ensure the study quality and compliance with the study plan and regulations.

The trial investigator agrees to provide data for review and reasonable resources during monitoring visits, to confirm adequacy of recorded data and the adherence to the study plan. Information in the CRFs and subject medical charts are verified by the monitor using the monitor's SOPs and in accordance with ISO 14155:2011 guidelines and good clinical practice (GCP) guidelines.

The trial investigator and study staff will agree to cooperate with the monitor as necessary by providing all necessary information. The trial investigator is required to add all relevant data to the subject's record. Relevant data include patient history, accompanying diseases, date of study start, attendance data, results of examinations, administration of medication and adverse events. The monitor will inspect records to ensure the rights and welfare of the subjects are protected. All data will be treated anonymously, only identifiable through the subject's identification number. All recorded data is verified by the trial investigator and by the monitor.

The monitoring will include conducting pre-investigation site visits, periodic monitoring visits, and study termination visits as appropriate. Records of each visit will be maintained and will include a statement of findings, conclusions and any actions taken to correct any deficiencies noted during the visit.

In situations requiring deviation from the protocol, the investigator will contact the sponsor. If possible, this contact will be made before implementing any deviation from the protocol. The sponsor will not approve deviations from the protocol but can help to avoid deviations or help to mitigate their implications. In all cases, contact with Sponsor must be made as soon as possible. Any deviations from the investigational plan will be documented on the appropriate Case Report Form. As required by applicable regulatory requirements notifications of deviations will be sent to Sponsors and Ethics Committees.

The investigational centre is required to archive subject's records and submit reports required by the governing regulations. After study completion, the trial investigator retains study documents for a period of at least 15 years after the latter of the following two dates: the last marketing approval has been obtained for the device and there are no pending marketing applications, or the investigation is terminated or completed. Study documents include a list for identifying the subjects, the subject's records with reference documents, documents from review by the Ethics Committee for the investigation, all protocol amendments, CRF copies and the informed consents of subjects.

13. Ethics

The clinical investigation plan with the patient information and consent forms will be submitted to an appropriately constituted Ethics Committee (EC) prior to the commencement of the study. A copy of the Ethics Committee opinion/approval will be provided to the sponsor prior to initiating the investigation.

The appropriate documents of the clinical study will be submitted to the Competent Authority (CA) prior to the commencement of the study. A copy of the CA approval will be provided to the investigator prior to initiating the investigation.

Upon completion of the investigation, the investigator or the Sponsor (as per national requirements) shall provide the EC and CA with a brief report of the outcome of the investigation.

Local Ethical committee's or Competent Authorities may ask for specific additions or modifications to the protocol to meet local requirements or concerns, these will be appended to this protocol and will be applicable only to the relevant countries or centres.

14. Data Handling and Record Keeping

The Sponsor will manage the study data in accordance with applicable regulations and Standard Operating Procedures. Data will be captured in Case Report Forms.

14.1. Data which is not Part of the Subject's Record or CRF

Electronic data (only identifiable through the subject's identification number) obtained during the tuning process and preliminary tests, log files, video and audio recordings, will be transmitted electronically in a secure fashion and stored by Sponsor. Other data collected during the study that includes test protocols and/or device history information not included on the CRF will be kept on logs, signed and dated by the entrant, and provided to the Sponsor.

14.2. Data Collection and Recording on Case Report Forms (CRFs)

The investigator or site authorized representative will document all observations and results on source documentation and subsequently transcribe data to CRFs, as applicable. The appropriate Case Report Forms will be completed by site study personnel (those authorized by the Investigator) in accordance with instructions provided by the Sponsor. All study personnel will be trained by the Sponsor on the proper completion of

CRFs, including methods for denoting changes and corrections, and need for signatures, initials, and dates.

The Investigator will ensure the accuracy, completeness, legibility and timeliness of the data entered in the CRFs and required reports to the sponsor by signing and dating CRFs as required.

14.3. Changes in the Investigation Plan – Amendments

Changes in the investigational plan are not planned to ensure consistency through the duration of the investigation and not confound data analysis, however some changes may be determined necessary as study information is collected.

Changes made to the investigational plan require submission to regulatory authorities and ethic committees for approval prior to implementation, unless the change does not affect the validity of the data, the patient risk/benefit relationship, and the scientific soundness of the plan, or the rights, safety or welfare of the patients. All changes made to the investigational plan will be thoroughly documented and summarized in periodic reports by the sponsor to regulatory authorities, as required.

14.4. Hardware and Software Supplied Data Acquisition

The hardware and software for data handling and keeping will meet applicable electronic data requirements for the electronic collection and storage of clinical data.

14.5. Instruction for the Documentation of the Investigation

The Investigator will maintain complete, accurate and current study records. During the monitoring visits, the study files are inspected for accuracy and completeness. After study completion or termination, study documentation is retained for a period of at least 15 years after the latter of the following two dates: the last marketing approval has been obtained for the device and there are no pending marketing applications, or the investigation is terminated or completed.

The investigator will ensure that the following study records are retained:

- List of subjects / identifying list
- Documentation of serious adverse events and serious unanticipated adverse events, and corresponding documentation to the ethics committee, subject, and regulatory authorities as required.

- Documentation about the receipt, disposition, and return of investigational devices
- Information on the investigational product, including the Investigator Brochure, Operating Manual, and Investigational Plan.
- Correspondence with the Sponsor and other involved institutions
- All patient records, informed consents, source documentation, patient completed worksheets, correspondence, and all other supporting documentation.
- Signed and dated Curriculum vitae of the Investigator as well other responsible participants including proof of at least 2 years' experience in conducting clinical investigations, and documentation of training and/or participation in investigator meetings.
- A signed investigator agreement
- Documentation of ethics committee approval and correspondence, including annual, final and other reports, and a copy of local EC procedures
- Copy of regulatory approval
- A signed and dated copy of the study protocol, including all amendments and documentation of deviations from the Investigational Plan.
- Signature list of authorized study personnel and documentation of their responsibilities
- Audit correspondence
- Blank copies of CRFs
- Blank copies of worksheets

14.6. Regulations for Archiving of Investigation Documents by the Trial Investigator and the Sponsor

Sponsor and contract organizations

All study documents relevant to the investigation are stored at the sponsor for at least 15 years after termination of the investigation.

Investigator

As noted above, after study completion or termination, study documentation is retained for a period of at least fifteen (15) years after the latter of the following two dates: the last marketing approval has been obtained for the device and there are no pending marketing applications, or the investigation is terminated or completed. The Investigator must notify the sponsor if the records are relocated at any point within that time to keep them advised of the location of these records.

15. Publication Policy

Any publication based on the results obtained at an individual site or group of sites must be approved by the sponsor. As outlined in the clinical study contract any manuscript or presentation must be provided to the Sponsor for approval in advance to submission and the sponsor has the right to reject publications.. All patient data will be rendered anonymous.

16. Appendices

Appendix	Description	Corresponding Document ID
Appendix A	Schedule of Procedures and Evaluations	• CIP-PRIMA-FS-M-App.A-Rev2
Appendix B	Screening Activities	• CIP-PRIMA-FS-M-App.B-Rev1
Appendix C	Endpoint Sub Protocol	• CIP-PRIMA-FS-M-App.C-1-Rev2 • CIP-PRIMA-FS-M-App.C-1A-Rev1 • CIP-PRIMA-FS-M-App.C-1B-Rev2 • CIP-PRIMA-FS-M-App.C-2A-Rev2 • CIP-PRIMA-FS-M-App.C3-Rev0 • CIP-PRIMA-FS-M-App.C3A-Rev0
Appendix D	Case Report Forms	• CIP-PRIMA-FS-M-App.D-1-Rev1 • CIP-PRIMA-FS-M-App.D-2-Rev1 • CIP-PRIMA-FS-M-App.D-3-Rev1 • CIP-PRIMA-FS-M-App.D-4-Rev1 • CIP-PRIMA-FS-M-App.D-5-Rev1 • CIP-PRIMA-FS-M-App.D-6-Rev1 • CIP-PRIMA-FS-M-App.D-7-Rev1 • CIP-PRIMA-FS-M-App.D-8-Rev1 • CIP-PRIMA-FS-M-App.D-9A-Rev1 • CIP-PRIMA-FS-M-App.D-9B-Rev1 • CIP-PRIMA-FS-M-App.D-10-Rev1 • CIP-PRIMA-FS-M-App.D-11-Rev1 • CIP-PRIMA-FS-M-App.D-12-Rev1 • CIP-PRIMA-FS-M-App.D-13-Rev1 • CIP-PRIMA-FS-M-App.D-14-Rev1 • CIP-PRIMA-FS-M-App.D-15-Rev1 • CIP-PRIMA-FS-M-App.D-16-Rev1 • CIP-PRIMA-FS-M-App.D-17-Rev1 • CIP-PRIMA-FS-M-App.D18-Rev0
Appendix E	Literature References	• CIP-PRIMA-FS-M-App.E-Rev1
Appendix F	Definitions	• CIP-PRIMA-FS-M-App.F-Rev1
Appendix G	Imaging and Testing	• CIP-PRIMA-FS-M-App.G-1-Rev1

		• CIP-PRIMA-FS-M-App.G-2-Rev1 • CIP-PRIMA-FS-M-App.G-3-Rev1 • CIP-PRIMA-FS-M-App.G-4-Rev1 • CIP-PRIMA-FS-M-App.G-5-Rev1 • CIP-PRIMA-FS-M-App.G-5A-Rev1 • CIP-PRIMA-FS-M-App.G-6-Rev1 • CIP-PRIMA-FS-M-App.G-6A-Rev1 • CIP-PRIMA-FS-M-App.G7 Rev0 • CIP-PRIMA-FS-M-App.G7A Rev0
Appendix H	Recruitment Material	• CIP-PRIMA-FS-M-App.H-Rev1

Note: the document identification number of documents in appendices may differ from the document number of the protocol main part. In addition the revision number may also differ from the main part. All documents in the Appendices are part of the protocol.