Non-Damaging Photothermal Therapy of Non-exudative Age Related Macular Degeneration

Study Protocol and Statistical Analysis Plan
NCT02569892

August 15, 2018

Title:
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Introduction

Age Related Macular Degeneration (AMD) is the leading cause of blindness and visual disability among patients exceeding 60 years of age in the western hemisphere. The clinical presentation of AMD ranges from soft drusen in patients with normal visual acuity to geographic atrophy or subfoveal choroidal neovascularization (CNVs), disciform scarring and eventually legal blindness.[1]

Approximately 10 to 15% of patients with AMD develop severe visual loss due to geographic atrophy characterized by the atrophy of retinal pigment epithelium, choriocapillaris and outer retina or due to exudative AMD. Nonexudative AMD is responsible for about 25% of the severe visual loss and the remaining is caused by neovascular AMD[2]. Fortunately, with the introduction of pharmacological anti-VEGF treatments to neovascular AMD, exudative AMD can be effectively treated, thereby maintaining good visual acuity for extended period of time. However, there is still no treatment for nonexudative AMD other than vitamin supplementation, and patients inevitably progress to advanced disease and associated visual loss.[3]

The cumulative incidence of new exudative or atrophic lesions in eyes initially free of advanced AMD has been estimated as 8.6% at one year, 16.4% at two years and 23.5% at three years.[4] The five-year risk of CNV occurrence in the fellow eye of patients who have already experienced CNV in the first eye, varies from 7% to 87% depending on the coexistence of four main risk factors (presence of five or more drusen, focal hyperpigmentation, one or more large drusen and systemic hypertension).

Owing to the risk of vision loss associated with the presence of large volume of drusen, retinal laser treatment was proposed to prevent progression to advanced AMD. Several clinical trials have been conducted to test the effect of laser photocoagulation on reabsorption of drusen in the macula.[5-12] Laser burns were applied to the retina, either directly to the drusen or following predefined patterns. Argon, krypton, dye or diode lasers have been used with varying levels of energy (ranging from sub-visible to faint or intense whitish retinal lesions). The assumption was that phagocytic cells or macrophages clearing the laser-induced debris in the retina, RPE and choroid could also reduce or eliminate the drusen. It was also speculated that laser could trigger release of cytokines and growth factors from the RPE, which may act on drusen regression.

A systematic review of all clinical trials using laser treatment of drusen demonstrated that there was a significant reduction of drusen over time. However there was also found a slight increase in the incidence of CNV and geographic atrophy, albeit not statistically significant [3]. This increase could be related to the fact that conventional photocoagulation used in most of these trials damaged the Bruch's membrane, consequently inducing CNV. Therefore, a non-damaging laser treatment strategy might be able to induce drusen regression without the known side effects of photocoagulation. This hypothesis is supported by the fact that "subthreshold" laser treatments of the drusen resulted in their reduction with much fewer side effects than with

conventional visible burns: 6 out of 63 eyes treated with visible burns developed CNV within 3 months of treatment, while no such CNV was reported for subthreshold treatment. Despite the drusen reduction, the treatment did not slow the progression to geographic atrophy or to CNV, compared to observation in this trial. This might be due to very small number (a few tens) of laser spots applied to the macula. Our approach might rectify this deficiency by applying higher density of the treatment: 500 non-damaging spots. [11-12]

Micropulse laser photocoagulation avoids the excessive heating which causes visible burns, tissue necrosis, and related collateral effects[13], while providing similar clinical benefits as conventional laser coagulation.[14 -19] However, the lack of a reliable titration for every patient and absence of visible endpoint makes it difficult for the physician to (a) know which retinal areas have been treated and (b) to ensure the adequate amount of laser energy in the treatment. In addition, the dense coverage of the retina with the sub-visible laser exposures typically requires more than 500 spots in the macula, which is difficult to accomplish without pattern scanning laser. These issues prevented acceptance of this technology in clinical practice.

We have developed the titration protocol for PASCAL laser, which ensures that pulse energy is within the range of clinical efficacy, but does not exceed the tissue damage threshold [21] in every patient. This protocol, called EndPoint Management, has been recently tested in a clinical trial, which demonstrated its safety and efficacy in treatment of Central Serous Retinopathy[22] using 30% energy settings. The trial demonstrated lack of tissue damage and excellent tissue response to the treatment, even after multiple retreatments. The average retreatment period in this trial was found to be 6 months.

We propose to use the same laser parameters for treatment of the macula in patients with early AMD to prevent drusen growth and advancement of the disease into geographic atrophy or neovascularization.

AIMS OF THE STUDY

1. To determine whether photothermal therapy (PTT) of the macula with EpM® reduces the volume of drusen in the macula.
2. To determine whether PTT decreases the incidence of advanced AMD (neovascular AMD or geographic atrophy).

The primary efficacy outcome measure will be the reduction in drusen volume in the central 3mm circle over 12, 18, 24 months in subjects treated with PTT, compared to observation alone.
The secondary efficacy outcomes after the month 12, 18, 24 of follow up will be:

- **Functional outcome**:
    - Mean change in visual acuity in both groups.
- **Anatomical outcome:**
    - Reduction of drusen growth;
    - Prevention of neovascular AMD;
    - Prevention of geographic atrophy based on OCT and FAF.

- **Safety Assessments**. Safety of the treatment will be assessed for ocular adverse event incidence (AEs) and serious AEs (SAEs), based on the reports of the patients and examination during or between visits until the month 24 of follow up. After 24 months, subjects will then be followed for an additional 3 years for observation
- **Serious adverse events** (SAEs) will be monitored continuously.

STUDY METHODS

Design:

- Prospective, Randomized Clinical Trial (RCT).
- 24 months with an additional 3 year observation follow up period. Subjects will be seen once a year and undergo non-invasive testing.
- Total patient recruitment 56 patients.
- Number of arms: 2 arms.
- Number of patients: 28 patients in each arm.

Patient Recruitment

1. Initial Assessment

The study will enroll 56 eyes in total. Patients will be initially assessed as part of their standard management and, if fulfilling all the inclusion criteria, will be referred to a Study Investigator.

At the initial assessment, the investigator will confirm that the patient has satisfied the eligibility criteria stated in the Study Protocol (SPR) and the study will be discussed in full with the study participant (SP). If interested in participating, the SP will be given a written informed consent to take home for further consideration. The patient will have a minimum of 24 hours to decide whether or not to take part in the study. All study procedures, will be explained to the SP by the investigator or staff member. The nature of the study will be also explained to the SP together with hazards of the study procedures, including any possible adverse events. The SP will be informed that he or she is free to terminate participation in the study for any reason.

Any patient unwilling to participate at this stage will be managed as part of the appropriate routine eye care pathway.

The study patient will undergo the Examination Procedures at the Baseline visit. The data from these tests will be used for study data analysis.

2. Examination Procedures at Baseline and Follow-up visits

(1) ETDRS best corrected visual acuity.
(2) Slit lamp biomicroscopy: dilated fundus examination with 78D Volk lens, intraocular pressure by Goldmann applanation tonometry.
(3) Spectral domain OCT (Cirrus SD-OCT): Macular/macular cube/Volume scan & average central retina thickness and Drusen volume.
(4) Fundus photography and autofluorescence.

The treatment will be randomised at this stage, and the SP will be allocated to arm A (treat) or arm B (observe). The 56 eyes will be randomly allocated to each of the two study arms, 28 in each arm. The SP will be given a trial number, and the treatment record will be coded. For patients where both eyes meet eligibility criteria both eyes will be enrolled with the Right Eye randomly assigned to active treatment arm or sham arm, with the Left Eye assigned to the opposite arm.

3. Treatment Visit:

The SP will undergo treatment within 14 days after the examinations are performed.

Patient-eligibility

Inclusion criteria:

1. Older than 60 years of age.
2. Male or female patients with nonexudative AMD with a drusen volume of of at least 0.03mm^3 on OCT within the central 3mm circle centered on the fovea.
3. Adequate pupil dilatation and clear media to perform color, red-free imaging, fundus autofluorescence imaging, and OCT imaging.
4. Able to give an informed consent.

Exclusion criteria:

1. Presence of signs of advanced AMD, such as CNV, haemorrhages or macular atrophy based on OCT and FAF.
2. Previous macular laser treatment.
3. Any previous ocular condition that may be associated with a risk of developing macular oedema.
4. Vitreomacular traction determined clinically and /or by OCT, which in the opinion of the investigator contributes to the macular oedema (associated or causing a detachment of the fovea).
5. Presence of other macular disease such as epiretinal membrane, macular telangiectasia.
6. Ocular or periocular infections.
7. Planned intra-ocular surgery within one year.
8. Patient is unavailable for follow-up visits.

Study Examination Procedure

Baseline:

1. Full patient history including age, gender, ethnic group, diabetes history, medical history, medication history, ocular history, driving history, smoking status.

Baseline and Follow-up visits (see table):

1. ETDRS BCVA
2. Slitlamp biomicroscopy:
   Dilated fundus examination with 78D Volk lens
   Intraocular pressure by Goldmann applanation tonometry
3. Spectral domain OCT
4. Optical coherence tomography angiography if available on site.
5. Fundus photography and autofluorescence.

Study Treatments Schedules:

Laser:

- Pupillary dilatation: Will be achieved using Tropicamide 1% and Phenylephrine 2.5%. One drop instilled every five minutes repeated three times.
- Anaesthesia: Topical anaesthetic will be applied to the cornea, prior to the commencement of treatment.
- Lens: Area centralis contact lens will be coupled to the cornea with 1% methylcellulose or equivalent.
- Laser system: Pascal® laser with 532 nm (green) or 577 nm (yellow) wavelength, with EndPoint Management Software (EpM) at 30%, 200 μm spot diameter and 0.25 spot-width spacing. A grid-pattern treatment will be applied to the area of retinal thickening as per OCT. The total number of spots should exceed 500, including the full macula grid + plus patterns of 2x2 inside the grid and patterns of 3x3 or 4x4 outside the grid.

Arm A:

Patients will be treated initially (Day 0) and every 6 months during the follow up, if meet retreatment criteria.

- **Number of laser spots:** >500. Customized grid pattern to cover area of drusen.
- **Spot size:** 200μm
- **Duration for titration:** 15 or 20 ms
- **Exposure:** Laser power will be titrated to produce a barely visible burn, considered a 100% at EpM®. For the treatment, energy is set at 30% to achieve non-damaging exposures.
- **Titration power range:** 100 to 200 mW
- **Spot spacing:** 0.25 spot-width-apart.
- **Retreatment criteria:**
  - Meet initial inclusion/exclusion criteria
  - Does not exhibit significant reduction in drusen volume 6 months after previous treatment. Significant is a 50% reduction in the cube root volume of drusen.

Arm B:

Patients will be treated with a sham laser (zero therapeutic power, only the aiming beam) and observed.

PATIENT FOLLOW-UP:

All participants will receive treatment at the initial treatment day and will have follow-up visits at 1 month (optional), 3, 6, 9, 12, 18, 24 months.

At the end of the 24 month period there will be an additional 3 year follow up. During the 3 year follow up, there would be no active component, the subjects will be seen once per year and undergo visual acuity testing and non-invasive retinal imaging to monitor for long term effects of treatment. This should not place a significant burden on the subjects since they are typically seen every 6 to 12 months for routine follow-up.

Best-corrected visual acuity (BCVA) using ETDRS charts at a distance of 4 meters, digital fundus photography, fundus autofluorescence, ocular coherence tomography (OCT), ocular coherence tomography angiography (OCTA when available on the site) will be carried out at baseline and at each follow-up visit.

TEST, treatment	Baseline	0	1 optional	3	6	12	18	24
Laser treatment		x			x	x	x	x
ETDRS visual acuity (BCVA)	x	x	x	x	x	x	x	x
Slitlamp	x	x	x	x	x	x	x	x
OCT	X	X	X	X	X	X	X	X
OCTA*	X	X	X	X	X	X	X	X
Digital Fundus Photography	X	X	X	X	X	X	X	X
Fundus autofluorescence	X	X	X	X	X	X	X	X

*OCTA will be done if available on site

STUDY RANDOMIZATION PROCEDURE

The subjects will be allocated to each arm of the study with simple randomization method using a computer-generated randomization list and sequentially number, sealed, opaque envelopes (SNSOE).

After a subject has signed informed consent, their name will be written on the selected envelope by the Clinical Trials Coordinator. The 56 eyes will

be randomly allocated to one of the two arms. The computer randomization will be done by the Clinical Trials Coordinator. The randomization table will be given to an independent person, who will sequentially label 56 envelopes, and enclose the written treatment type within the envelope. The study arm will be coded numerically for each subject.

METHOD OF STATISTICAL ANALYSIS

The data will be analysed using analysis of covariance, adjusting for baseline and disease severity. Results will be presented as differences between the treatment arms with their associated 95% confidence intervals, and non- significant effects interpreted in the context of these and the limited power of the study.

SAMPLE SIZE:

We estimated our sample size based on previous comparable publications that included approximately 50 eyes on average.[11-12]

EFFICACY MEASURES:

Primary Outcome:

- Reduction in drusen volume in arm A compared to arm B.

Secondary Outcomes:

- Mean change in visual acuity (ETDRS letters)
- Mean change in average central retinal thickness (ACRT) after 12, 18, 24 months of follow up.
- The proportion of patients with ACRT < 300 µm on Spectral domain OCT after 12, 18, 24 months of follow up
- Conversion into GA or CNV

SAFETY MEASURES:

- Monitoring of adverse events (AEs) and serious adverse effects (SAEs) (the incidence of ocular AEs and SAEs).
- Assessment of the retinal autofluorescence to identify any laser burn.
- Signs of any laser burn identified at RPE-photoreceptors layers on DRI-OCT.

ADVERSE EFFECTS:

- Any medical incidence in patients who received laser that could be associated with the treatment delivered in the research study.
- Any temporal or transitory adverse effect that has relationship to the study therapy.

REPORTING ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS

- With any AE, we will treat the SP as appropriate to prevent further complications and to potentially resolve the event.
- SAEs and AE will be reported immediately (when the subject is in the office, if possible or within 24 hours of learning of the event) to the principal investigator, study coordinator and sponsor. The SP subject will be referred for further medical treatment if required.
- Follow-up reports on AEs should indicate whether the AE is presumed to be device-related, or a result of other factors, and should be recorded on the Adverse Events Report. The Adverse Events Report should be completed each time the subject is seen during the management of the incident and at resolution of the incident.
- All AEs occurring from the time of written informed consent throughout the course of the study (end of study is defined as the end of the scan acquisition) will be recorded at the study site.
- The AE should be made to describe it in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

All the adverse events shall be recorded in detail as specified below:

Name (Type)	The common name of the adverse event that appeared shall be written down.	
Date of onset	The first date that the physician in charge found the adverse event shall be written down.	
Causal relation	Write down probable causes, and classify the causal relation with the test device depending on the presence or absence of the causal relationship as defined below. The adverse events that are judged to have no relation with the test devises are classified as complications; all the others are classified as adverse device effects.	
	Probably not related	The adverse event is definitely related to other than the test device. (Complication)
	Possibly related	The adverse event is possibly related to the test device; the causal relationship with the test devices is fully undeniable. (Adverse device effect)
	Probably related	The cause of the adverse event cannot be located. However, the adverse event is probably related to the test device. (Adverse device effect)
	Definitely related	The adverse event is definitely related to the test device. (Adverse device effect).
Severity	The severity shall be classified into mild, moderate and severe based on the criteria:	
	Mild	The symptom is mild and expected to heal soon.

	Moderate	The symptom is described as neither mild nor severe.
	Severe	The finding is serious and expected to interfere with the subject's daily life depending on the subject's physical predisposition or the circumstances under which the adverse event appeared.
Symptom, progress and treatment	Necessity for treatment and progress from the detection of the adverse event and the determination of outcome shall be written down.	
Outcome	The classification into "healed", "unchanged", "aggravated", or "death" and the outcome date shall be written down. If the subject died, statement of death shall be made.	
Views on the adverse event	Views on the adverse event by the physician in charge shall be written down. Omission is allowed if there are no special comments.	

POTENTIAL RISKS:

- Complications of conventional laser therapy including marked vision loss, paracentral scotomas or accidental application of laser in the fovea. There is limited data regarding potential risks of photothermal therapy, however, due to its non-damaging nature, it is expected to be safer than conventional photocoagulation.

STUDY PATIENT DISPOSITION

Completed SP: A completed SP is one who has not been discontinued from the study and has completed all study related procedures.

Discontinued SP: SP may be discontinued prior to their completion of the study due to:

- subject request
- adverse events
- protocol violations
- administrative reasons (e.g., inability to continue, lost to follow up)
- termination of the study

Note: In addition, any SP may be discontinued for any sound medical reason. Notification of a SP discontinuation and the reason for discontinuation will be clearly documented.

STUDY TERMINATION

The study may be stopped at any time by the investigator, the sponsor, and/or study monitor with appropriate notification.

STUDY COMPLIANCE

An investigator should not deviate from the clinical protocol. Should a deviation occur the date of and reason for deviations will be documented by the monitor via the monitoring report and further detail may be requested from the investigator. Deviations will be reported to the sponsor immediately.

MONITORING AND QUALITY ASSURANCE

Study Monitoring

The designated study monitor will review the protocol, regulatory obligations, and other material or equipment relevant to the conduct of the study prior to the start of the study with the principal investigator/co-investigator(s) and pertinent study staff. Monitoring visits will occur as necessary during the course of the investigation to verify:

• The rights and well-being of subjects are protected.
• The conduct of the investigation is in compliance with the currently approved protocol.
• The integrity of the data.
• Device accountability adequate study documentation.

CONFIDENTIALITY

Recording of Data

SP data recorded during the study will be documented in the patient's clinical file. In the data analysis the SP will only be identified by the subject number, and by their initials if also required. If, as an exception, it is necessary for safety or regulatory reasons to identify the SP, the sponsor or its representative, and the investigator are bound to keep this information confidential.

All personal SP data collected and processed for the purposes of this study will be maintained by the investigator and his staff with adequate precautions as to ensure that the confidentiality of the data in accordance with local laws and regulations.

PUBLICATION POLICY

Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript.

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