Clinical Trial Protocol PEELING

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"Prospective, randomized, controlled and single-blind study assessing the benefit/risk ratio of internal limiting membrane (ILM) peeling during Epimacular Membrane (EMM) surgery."

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PROTOCOL SYNOPSIS

Title	Prospective, randomized, controlled and single-blind study assessing the benefit/risk ratio of internal limiting membrane (ILM) peeling during Epimacular Membrane (EMM) surgery
Key word(s)	Idiopathic epimacular membrane; internal limiting membrane peeling, microscotomas
Sponsor	**CHU DE NANTES (Nantes University Hospital)**
Coordinator	Prof. Weber (Ophthalmology department – CHU de Nantes)
Study center(s)	National study, five centers involved in addition to Nantes : - Ophthalmology Department of Lariboisiere Hospital and Cochin Hospital (Prof. Ramin Tadayoni) - Ophthalmology Department of Dijon University Hospital (Prof. Catherine Creuzot-Garcher) - Fondation Ophtalmologique Adolphe de Rothschild (Dr. Yannick Le Mer) - Polyclinique de l'Atlantique de Saint-Herblain (Dr Julien Perol , Dr Alexandre Bourhis, Dr François Lignereux) -Clinique Sourdille de Nantes (Dr Frank Becquet)
Type	Biomedical research non health product
Study duration	- Overall duration of the study: 90 months - Enrollment period: 78 months - Patient treatment period: 1 hour - Patient follow-up period: 12 months
Design	- Multi-center - Controlled - Randomized - Single-blind - Prospective
Objectives	**Primary study objective**: to compare the difference in microscotomas before surgery and 6 months after surgery between the two groups. **Secondary objective(s):** * Study of anatomical and functional changes of the retina: - Analysis of the difference between the number of

	microscotomas found before surgery and the number of microscotomas found at 1 and 12 months. - Analysis of the type of microscotomas (relative or absolute) in both groups and at different times: preoperatively, at 1, 6 and 12 months. - Analysis of the evolution of the mean visual acuity between preoperative visual acuity and visual acuity at 1, 6 and 12 months in both groups. - Analysis of the evolution of retinal sensitivity of the 29 points between the inclusion visit and at 1, 6 and 12 months. - Analysis of the symptoms ("Patient discomfort" questionnaire) at the inclusion visit and at 1 month, 6 months and 12 months. - Study of the correlation between the gripping areas of the EMM and the ILM and the location of the new microscotoma(s) that appeared at 1 and 6 months, depending on the surgeon's surgery data and the centralized processing of the surgery video. - Analysis of the trend (persistence/disappearance) of the number of microscotomas at months 1 and 6 in connection with the EMM, predating surgery. - Study of the correlation between visual acuity and retinal sensitivity (the central point and the average of the five most central points) at different times. - Analysis of the percentage of anomalies of the nerve fiber layer (DONFL or SANFL) detectable by a frontal OCT at 1, 6 and 12 months with analysis of the area in question. - Analysis of the association between anomalies of the SANFL nerve fiber layer and the microscotoma(s) at 1, 6 and 12 months. - Analysis of data from the OCT B scan: Overall central retinal thickness of 1000 microns, integrity of the junction line between the internal and external segments of the photoreceptor at the fovea, integrity of the outer limiting membrane at the fovea, thickness of the outer layer of the article of the photoreceptors at the fovea, thickness of the ganglion cell layer in regards to microscotomas at different times. - Analysis of the association between these anomalies from the OCT B scan (described above) and the visual acuity between these anomalies and the presence of

	microscotomas at 1, 6 and 12 months. * Study the rate of EMM recurrence (at M12) between the 2 groups.
Projected number of subjects	53 randomized eyes (1eye/patient) per arm that means 106 randomized eyes (106 randomized patients) in total and a maximum of 222 included patients (116 spontaneous peeling)
Schedule of visits and tests	The visits for this trial are those planned for patients receiving EMM surgical operation, namely: Selection/Inclusion visit : D-90 to D-7 This visit can be split in two according to the requirements of the investigator and/or the patient. *Full information about the trial *Verification of the inclusion and non-inclusion criteria *Obtaining the signed informed consent (the same day or after a period of reflection) *Medical and surgical history - *Examination: Visual acuity measured on the ETDRS scale, near vision (Parinaud), spectral domain optical coherence tomography (SD-OCT), microperimetry and pre-operative: "Patient discomfort" questionnaire (Appendix 7), an assessment of the appearance of the lens at the slit lamp, examination of the fundus after pupillary dilation, biomicroscopic examination of the anterior segment, retinal photography. Surgery visit D0: * List of all the surgical procedures * Randomization for ILM peeling or not, in the operating room after dyeing of the ILM by the Membraneblue-Dual® (Picture of the macula). An anonymous video of the surgery will be sent to Nantes for centralized processing of the analysis of the EMM's grip areas. To avoid bias, the follow-up visits will be made by an ophthalmologist and/or an orthoptist who will not know what action has been performed. Follow-up visit M1 (1 month after the surgery ± 7 days) *Examination: Visual acuity measured on the ETDRS scale, near vision (Parinaud), spectral domain optical coherence tomography (SD-OCT), Microscopic examination of the eye, microperimetry, fundus photography and post-operative "Patient discomfort" questionnaire (Appendix 8). Biomicroscopic examination of the anterior segment, retinal photography. *AE

	Follow-up visit M6 (6 months after the surgery ± 15 days) *Examination: Visual acuity measured on the ETDRS scale, near vision (Parinaud), spectral domain optical coherence tomography (SD-OCT), Microscopic examination of the eye, microperimetry, fundus photography and post-operative: "Patient discomfort" questionnaire (Appendix 8). Biomicroscopic examination of the anterior segment, retinal photography. *AE End of study visit M12 (12 months after the surgery ± 15 days) *Examination: Visual acuity measured on the ETDRS scale, near vision (Parinaud), spectral domain optical coherence tomography (SD-OCT), Microscopic examination of the eye, microperimetry, fundus photography and post-operative "Patient discomfort" questionnaire (Appendix 8), Biomicroscopic examination of the anterior segment, retinal photography. *AE
Main inclusion criteria, non-inclusion criteria	**Inclusion Criteria** • Adult patients (>18 years old) and female without childbearing potential or active contraception (intra-uterine device, contraceptive pill or contraceptive implant). • Patients with an idiopathic symptomatic epimacular membrane; for patients with both eyes affected, the eye treated in the protocol will be the one which is most severely affected. • Pseudophakic patients with transparent posterior capsule or open capsule or lensed patients with age-related cataracts • Patients with social security • Patients able to understand and follow the trial instructions • Patients who have signed an informed consent **Non - inclusion** • Patient with other retinal pathologies such as age related macular degeneration ("AMD"), retinal vein occlusion, diabetic retinopathy, glaucoma with macular visual field defect • Patients with uveitis or history of uveitis • Patients with any recent eye injuries or eye surgeries (<6 months) • Patients participating in interventional clinical trial • Pregnant or breast feeding women • Vulnerable people : persons deprived of liberty; under trusteeship or under curatorship

Procedure in the study	The surgical procedure under study is ILM peeling. It is conducted at the end of EMM surgery. The surgical treatment therefore includes a common part for all patients, and the occurrence, or not, according to randomization, of ILM peeling. <u>For patients requiring this, cataract surgery will be performed at the same time.</u> <u>Common surgical procedure (Appendix 5):</u> For phakic eyes with cataract • phacoemulsification and implantation of a posterior chamber intraocular lens For all patients: • Central and peripheral 25 Gauge vitrectomy • dissection of the epimacular membrane • injection of Membraneblue-Dual® according to protocol, wait of 1 minute with the infusion line closed, and then suction of surplus and washing of the vitreous cavity • Intraoperative picture to see the possible spontaneous ILM peeling • If no spontaneous ILM peeling, the patient will be randomized at the operating block <u>Specific surgical procedure:</u> • • Randomization into two groups: - Arm 1: "no peeling", where the ILM peeling will not be made - Arm 2: "active peeling", where the ILM peeling will be made At the end of the surgery, the retinal periphery will be checked, as is usual after any vitreoretinal surgery.
Reference therapy (if appropriate)	Peeling of the internal limiting membrane systematically associated with EMM.
Primary endpoint	The primary endpoint of the study is the difference in microscotomas between the inclusion visit and the visit at 6 months after surgery.
Secondary endpoint(s)	• Visual acuity (VA) measured on the ETDRS scale and near vision (Parinaud) (inclusion visit, 1 month, 6 months and 12 months after surgery) • Number and types of microscotomas by microperimetry (before and after surgery)

	• Mean retinal sensitivity by microperimetry before and after surgery (at months 1, 6 and 12) • Questionnaire visual Patient discomfort: Symptoms and subjective improvement before and after surgery (at months 1, 6 and 12) • Incidence of changes of the retinal nerve fiber layer SD by OCT Analysis (B scan and C Scan) before and after surgery • Sinusoid (IS/OS) line disruption by OCT Analysis (B scan and C Scan) before and after surgery • Mean retinal thickness by OCT Analysis (B scan) before and after surgery • Retinal nerve fiber layer thickness by OCT Analysis (B scan) before and after surgery • Outer segment photoreceptor thickness by OCT Analysis (B scan) before and after surgery • Recurrence of EMM by OCT Analysis (B scan and C Scan) • Operative report and the video recording area of EMM and ILM gripping (study of the correlation with the microsoctoma(s)
Statistical considerations	Analysis of the primary endpoint: the main criterion is the difference between the number of microscotomas measured before surgery and the number of microscotomas measured at 6 months (number between 0 and 29). The mean difference will be calculated in each of two groups and compared using a mixed model of linear regression to take into account the stratification of the randomization at the center (the center will be considered as a random effect) and ajustment for the preoperative number of microscotomas.
Ancillary Study Others Analyses	Study of patients with spontaneous ILM peeling The aim of this study is to compare primary and secondary endpoints between patients with spontaneous peeling and patients in the active peeling group at inclusion visit and 1, 6 and 12 months after surgery.

SIGNATURE PAGE

The signatures below constitute approval of the protocol entitled "*Prospective, randomized, controlled and single-blind study assessing the benefit/risk ratio of internal limiting membrane (ILM) peeling during Epimacular Membrane (EMM) surgery".*

SPONSOR SIGNATURE:

The sponsor agrees to comply with the laws and regulations on clinical trials for the conduct of the above mentioned study and agrees to abide by all provisions set forth therein.

Name and capacity of the signatory representative:	**Date:**	**Signature:**
Anne-Claire de Reboul Centre Hospitalier Universitaire de Nantes 5, Allée de l'île Gloriette 44093 Nantes cedex 1 (FRANCE)		

INVESTIGATOR'S SIGNATURE:

I have read all the pages of the above-mentioned study protocol and agree to abide by all provisions set forth therein. I confirm that this protocol contains all the information necessary for the conduct of the study.

I agree to comply with the Declaration of Helsinki, the guideline for Good Clinical Practice of the International Conference on Harmonization (ICH-E6), the French national guideline "Règles de bonnes pratiques cliniques pour les recherches biomédicales portant sur des médicaments à usage humain" (Dated 24 November 2006), national laws and regulations, and the European Clinical Trials Directives 2001/20/EC and 2005/28/EC for the conduct of the above-mentioned study.

I agree for the investigators and other qualified members of my staff to have access to the copies of this protocol and documents concerning the conduct of the study so that they abide by all provisions set forth therein.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the study.

I agree that my identity may be subject to data processing by the sponsor or on its behalf.

Coordinator:		
Prof. Weber Ophthalmology Department Centre Hospitalier Universitaire de Nantes 1 place Alexis Ricordeau 44093 Nantes cedex 1 (FRANCE)	**Date:**	**Signature:**

Principal investigator:		
Prof. Ramin Tadayoni *Ophthalmology Department of Lariboisiere Hospitl and Cochin Hospital, Paris*	**Date:**	**Signature:**
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LIST OF ABBREVIATIONS

AE	Adverse event
AMD	Age related Macular Degeneration
ANSM	Agence Nationale de Securité du Médicament et des produits de santé
AREDS	Age Related Eye Disease Study
BPC	Bonnes Pratiques Cliniques (=GPC)
CIB	Clinical Investigator's Brochure
CNIL	Commission Nationale de l'Informatique et des Libertés
CRA	Clinical Research Assistant
CRF	Case Report Form
CRN	Clinical Research Nurse
CRT	Clinical Research Technician
DONFL	Dissociation of Optic nerve fiber layer
eCRF	Electronic Case Report Form
EMM	Epimacular membrane
ETDRS	Early Treatment Diabetic Retinopathy Study
EUDRACT	European Union Drug Regulatory Agency Clinical Trial
FDA	Food and Drug Administration
GCP	Good Clinical Practice (=BPC)
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ILM	internal limiting membrane
INSERM	Institut National de la Santé et de la Recherche Médicale
ISC	Independent Safety Committee
MA	Marketing Authorization
MH	Macular hole
MR	Méthodologie de Référence
OCT	Optical Coherence Tomography
PI	Principal Investigator
SD OCT	Spectral Domain Optical Coherence Tomography
SLO	Scanning Laser Ophthalmoscope
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
VA	Visual acuity
WHO	World Health Organization

CONTENTS

INTRODUCTION

The epimacular membrane (EMM) is a degenerative condition associated with age, with a variable impact on vision. Treatment is surgery based and consists of a vitrectomy followed by a peeling of the epimacular membrane using a microgripper. Peeling of the internal limiting membrane (ILM) is an adjuvant action that is now frequently practiced and which is expected to increase the success rate of EMM surgery by reducing the risk of recurrence of EMM. Although ILM peeling does not seem to have an adverse effect on visual acuity, it is not totally without consequence, it involves the risk of histological disorganization of the retina at the origin of one or several microscotomas, which are themselves responsible for a final visual discomfort. These microscotomas, resulting in the perception of somewhat black spots visible near the fixed point or the fixed image, may be highlighted by microperimetry and would be a loss of functional opportunity for the patient.

In addition, recurrence of EMM, which the ILM peeling is supposed to diminish, does not alter the vision in half the patients. Furthermore, for those patients who are functionally affected by any such recurrence, a second epimacular membrane peeling surgery can be done.

The main objective of this study is to compare the difference in microscotoma(s) before surgery and 6 months later, between an "active ILM peeling" group and a "no ILM peeling" group. Given the more invasive nature of ILM peeling, we believe that the rate of microscotomas in these patients is higher than those without peeling.

1 JUSTIFICATION OF THE STUDY

1.1 POSITIONING OF THE STUDY

Epimacular membrane (EMM) is a common condition characterized by a fibrocellular proliferation developing at the surface of the macula.
Treatment is surgery based, including a vitrectomy then a peeling of the epimacular membrane using a microforceps. The internal limiting membrane is sometimes adherent to the epimacular membrane and removed with it (spontaneous peeling), but it can remain in place and would constitute a risk of recurrence of EMM.
Peeling of the internal limiting membrane is now often practiced routinely by surgeons in EMM surgery. This treatment is an adjuvant action expected to increase the success rate of EMM surgery, but no prospective study has been published to date on this subject. Moreover, even in case of recurrence of EMM, vision is only altered in half the patients. In these cases, if visual loss occurs, a second EMM surgery is possible.
It is important to clarify the potential usefulness of peeling the internal limiting membrane (ILM), because even if this action does not appear to have any adverse effect on visual acuity, it is not totally without consequence. It involves risks associated with this surgical procedure (involuntary retinal tear, phototraumatism) (1) and the risk of histological disorganization of the retina (2), which is at the origin of one or more microscotomas. These microscotomas cause a definitive visual discomfort. Such microscotomas would entail a loss of functional opportunity for the patient because they cause the perception of black spots of varying degrees visible around the fixed point or the fixed image.
After epimacular membrane surgery, anatomical abnormalities of the nerve fiber layer are observed. Mechanical traction during peeling of the internal limiting membrane would be a possible hypothesis explaining these anomalies (3). One hypothesis is that the tensions created by the peeling of the EMM and/or ILM lead to a dissociation of the nerve fibers and thus damage to the Müller cells that hold the fibers together (4). These postoperative anatomical abnormalities can be viewed on photographs with blue filter or on postoperative analysis of the macular profile on an Optical Coherence Tomography (OCT) (5).

Microperimetry is a noninvasive test that allows for a real-time qualitative and quantitative assessment of visual functions. It helps define the retinal attachment point and the threshold of differential sensitivity of the retina with extreme precision. We can now study, thanks to microperimetry, the anatomical lesion and the functional impairment in various retinal pathologies (6), including OCT SLO (Scanning Laser Ophthalmoscope) microperimetry which couples microperimetry data with optical coherence tomography (OCT) data (7).
Abnormalities (microscotomas) detected by microperimetry were observed in patients after macular surgery and peeling of the internal limiting membrane (8). These abnormalities could explain the visual discomfort reported by some patients undergoing EMM and are not detected by conventional methods for the assessment of visual function (measurement of visual acuity and/or visual field).

By contrast, another study by Ito et al. (9) found no correlation between the presence of microscotomas and peeling. In their series, 36 (54%) eyes that underwent peeling presented an aspect of "DONFL" (Separation of nerve fibers of the optic nerve) to the surface of the retina. No significant difference in microscotoma was found between the eyes peeled, with or without "DONFL" aspect and unpeeled eyes. However, this retrospective and nonrandomized study examined the anatomical and functional consequences of epiretinal membrane peeling in another macular pathology: macular hole (MH). The study population was therefore different from that of epimacular membranes.
Very few published studies analyze the presence of microscotomas after ILM peeling. Gass et al. (10), in a series of 105 patients, found the presence of defects of peripheral vision in only one eye (1%). The authors suggest that the peripheral visual field defects are due to traction on the peripapillary region during the peeling of posterior vitreous.
To date, no randomized study comparing the presence of microscotomas in patients after surgery of the epimacular membrane with and without ILM peeling has been published. This explains our wish to carry out a prospective randomized study.
The search for the number and type of microscotoma(s) by microperimetry after EMM surgery with or without peeling of the internal limiting membrane will clarify the potentially deleterious effects of ILM peeling.
If the existence of these anomalies is demonstrated more frequently when the ILM is peeled off, it could jeopardize the interest of systematic ILM peeling which could then be preferably reserved for patients in whom the benefit of the act exceeds its side effects (especially in case of recurrent EMM).

These abnormalities could explain the visual discomfort sometimes described by patients undergoing EMM; which is why we will, at the same time, study the discomfort felt by the patient before and after surgery, using a pre and postoperative questionnaire.

This study will also evaluate the long term results of modern EMM surgery in terms of visual acuity, central and pericentral retinal sensitivity and the recurrence rate of EMM according to whether ILM peeling occurred or not.

This study will further refine the analysis of anatomical abnormalities visualized by SD-OCT (B and C scans) and their correlation with the visual outcome of this surgery and the presence of microscotoma(s).

The analysis of video recordings of interventions will help clarify the correlation between the microscotoma(s) and gripping the EMM and the ILM, which is not yet reported in the literature but will be identified by our retrospective study.

Furthermore, in an ancillary study, the evolution of patients with spontaneous ILM peeling will be led. The aim of this study is to compare primary and secondary endpoints between patients with spontaneous peeling and patients in the active peeling group at inclusion visit and 1, 6 and 12 months after surgery.

1.2 BENEFITS AND RISKS FOR SUBJECTS

1.2.1 Benefits

1.2.1.1 Individual benefits

The expected individual benefit is an improved visual comfort of patients operated without active peeling of the internal limiting membrane.
This benefit can be evaluated subjectively by the patient, but also via microperimetry, which tallies the number of microscotomas. Finally an anatomic evaluation using optical coherence tomography will assess the presence or absence of histological disruption of the macular retina.
The individual benefit will be zero for patients in the "active peeling" of the internal limiting membrane arm, who will receive the standard operating procedure applied to patients with epimacular membrane.

1.2.1.2 Collective benefits

If it is scientifically proved that the peeling of the internal limiting membrane increases patient discomfort, then it will be difficult to justify the continuation of this action in the practice of EMM surgery. The collective benefit will equate to improved patient care in functional terms.

1.2.2 Risks

1.2.2.1 Individual Risks

- ***Physical risks and constraints***

Currently, ILM peeling during EMM surgery is common. Non-fulfillment of this gesture in the "no peel" group will not exhibit any additional physical stress. The postoperative period is the same in both groups. Finally, the length of stay will not be modified.
Moreover, the additional tests provided during control consultations are those already conducted as a common practice in this context. Only microperimetry is unusual, but it does not expose patients to any invasive procedure or any adverse effect, even minimal. Note that this test is short, lasting about 10 minutes.

- ***Disease-related risks***

The only benefit of actively peeling the internal limiting membrane reported in studies to date is the decrease in the rate of recurrence of epiretinal membranes. So patients in the group "without ILM peeling" will be at higher risk of EMM recurrence than those in the group "with ILM peeling".

That data are inconsistent, because they were obtained on small retrospective samples. Kwok reports, for example, 17.6% of recurrences at 18 months after surgery (in 17 patients) in the "unpeeled" group vs. 0% in the "active peeling" group (25 patients) (11). Fang found a recurrence of 12.6% in the absence of peeling (of 8 patients) (12). Shimada reported in a prospective study of 1 year: 16.3% recurrence in the "unpeeled" group (17 of 104 eyes) vs. 0% of "active peeling" (0 of 142 eyes) (13).

- ***Surgery-related risks***

These are the side effects listed in Section 8.4 "List of expected AE":

- endophthalmitis (eye infection) (1-3 in 1000),
- changes in the macula, tear(s) of the retina, retinal detachment (3%) that may occur after surgery and require additional treatment by reoperation and/or laser,
- clouding of the cornea,
- central retinal edema,
- retinal burn from the illumination of the surgical microscope,
- inadequately sealed scar,
- partial collapse of the upper eyelid,
- subconjunctival hemorrhage or of eyelid,
- perception of floaters,
- increased sensitivity to light,
- inflammation of the eye,
- increased intra-ocular pressure.

1.2.3 Benefit-risk balance

For patients in the "no ILM peeling" group, individual expected benefit from not peeling the inner limiting membrane corresponds to a decrease in the number of microscotomas behind a visual discomfort for patients.
The main risk associated with this peeling is a higher incidence in the number of recurrences of the EMM, while requiring a new operation, but with no definitive functionality as is the case for microscotomas.
For patients in the "active ILM peeling" group, the risk/benefit ratio is zero because they will undergo the standard EMM surgery procedure.

1.3 DESCRIPTION AND JUSTIFICATION OF THE TREATMENT PLAN

The surgery under consideration is ILM peeling. It is performed at the end of EMM surgery. The surgical treatment therefore includes a common part for all patients, and the occurrence, or not, according to randomization, of ILM peeling.

Common surgical procedure: (ref Standard Operative Procedure Appendix 5 and surgical flowchart Appendix 6)

- For phakic eyes with cataract phacoemulsification and implantation of a posterior chamber intraocular lens

- For all patients:
  - central and peripheral 25 Gauge vitrectomy
  - epimacular dissection of the membrane with an Eckardt forceps (single model provided for the study)
  - injection of Membraneblue-Dual® provided for the study, wait of 1 minute, then surplus extraction and washing of the vitreous cavity following the standard operating procedure set out in Appendix 5 and 6
  - assessment of the integrity of the ILM and intraoperative photograph.

In some patients (up to 1 in 3 - ref 21), the ILM will withdraw spontaneously. "Spontaneous peeling" will be deemed to occur when the spontaneously peeled surface is greater than half of a circle of two papillary diameters of radius centered in the fovea. These patients are not randomized into the study but they will be included in the ancillary study.

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Specific surgical procedure:

- Patients will be randomized into two groups:
  - Group 1: "no peeling" where the ILM peeling will not be made
  - Group 2: "active peeling" where the ILM peeling is performed on at least two papillary diameters around the fovea (radius), which corresponds to a "circle" of 4 papillary diameters diameter

At the end of the surgery, we will check the retinal periphery, as in any vitreoretinal surgery.

Justifications:

- of the choice of Membraneblue-Dual® for coloring :

ILM peeling is possible without the use of dye; however, in these cases it is often incomplete. In fact, available data suggests that the rate of incomplete peeling is 66% when done without dye (14).
Membraneblue-Dual® used for ILM coloring, has a CE mark.
To avoid bias, the Eckardt forceps for dissection of the epimacular membrane and the dye Membraneblue-Dual® will be provided to all centers, as well as standard operating procedure for the coloring of the eye (see Appendix 5).

- *performing cataract surgery in phakic patients:*

The onset or continued worsening of postoperative cataracts interferes with the visual recovery and disrupts the assessment of visual function including retinal sensitivity microperimetry (15 to 17).

EMM mainly affects patients aged over 60. Most of these patients already have preoperative bilateral crystalline lens opalescence. The worsening of the cataract in the year following vitrectomy is the most common surgery complication of epimacular membranes. Combined cataract and vitrectomy surgery for the epimacular membrane is a commonly used technique that provides good functional results (18, 19).

- *Definition of the "active peeling" group*

ILM peeling of at least two papillary diameters of radius around the fovea, which corresponds to a "circle" of 4 papillary diameters in diameter.

- *Definition of the " spontaneous peeling" group:*

"Spontaneous peeling" will be deemed to occur when the spontaneously peeled surface will be greater than half of a circle of two papillary diameters of radius centered in the fovea. These patients are not randomized into the study but they will be included in the ancillary study.

The bibliographical references are appended to the document.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1. OBJECTIVE AND PRIMARY ENDPOINT

2.1.1 Main objective

Compare microscotoma differences between the "active peeling of the ILM" group and the "no ILM peeling" group between the inclusion visit and 6 months after surgery.

2.1.2 Primary endpoint

The main criterion is the difference between the number of microscotomas (sensitivity <10 dB) found before surgery and the number of microscotomas found at 6 months (number between 0 and 29).

2.2 OBJECTIVES AND SECONDARY ENDPOINTS

2.2.1 Secondary objectives

* Study of anatomical and functional changes of the retina:

- Analysis of the difference between the number of microscotomas found before surgery and the number of microscotomas found at 1 and 12 months.
- Analysis of the type of microscotomas (relative or absolute) in both groups and at different times: preoperatively, at 1, 6 and 12 months.
- Analysis of the evolution of the mean visual acuity between preoperative visual acuity and visual acuity at 1, 6 and 12 months in both groups.
- Analysis of the evolution of retinal sensitivity of the 29 points between the inclusion visit and at 1, 6 and 12 months.
- Analysis of the symptoms ("Patient discomfort" questionnaire) at the inclusion visit and at 1 month, 6 months and 12 months.
- Study of the correlation between the gripping areas of the EMM and the ILM and the location of the new microscotoma(s) that appeared at 1 and 6 months, depending on the surgeon's surgery data and the centralized processing of the surgery video.
- Analysis of the trend (persistence/disappearance) of the number of microscotomas at months 1 and 6 in connection with the EMM, predating surgery.

- Study of the correlation between visual acuity and retinal sensitivity (the central point and the average of the five most central points) at different times.

- Analysis of the percentage of anomalies of the nerve fiber layer (DONFL or SANFL) detectable by a frontal OCT at 1, 6 and 12 months with analysis of the area in question.

- Analysis of the association between anomalies of the SANFL nerve fiber layer and the microscotoma(s) at 1, 6 and 12 months.

- Analysis of data from the OCT B scan: Overall central retinal thickness of 1000 microns, integrity of the junction line between the internal and external segments of the photoreceptor at the fovea, integrity of the outer limiting membrane at the fovea, thickness of the outer layer of the article of the photoreceptors at the fovea, thickness of the ganglion cell layer in regard to microscotomas at different times.

- Analysis of the association between these anomalies from the OCT B scan (described above) and the visual acuity between these anomalies and the presence of microscotomas at 1, 6 and 12 months.

* Study the rate of EMM recurrence (at M12) between the 2 groups

2.2.2 Secondary endpoints

- Visual acuity (VA) measured on the ETDRS scale and near vision (Parinaud) (inclusion visit, 1 month, 6 months and 12 months after surgery)
- Number and types of microscotomas by microperimetry (before and after surgery)
- Mean retinal sensitivity by microperimetry before and after surgery (at months 1, 6 and 12)
- Patient visual discomfort questionnaire: Symptoms and subjective improvement before and after surgery (at months 1, 6 and 12)
- Incidence of changes of the retinal nerve fiber layer SD by OCT Analysis (B scan and C Scan) before and after surgery.
- Sinusoid (IS/OS) line disruption by OCT Analysis (B scan and C Scan) before and after surgery
- Mean retinal thickness by OCT Analysis (B scan) before and after surgery
- Retinal nerve fiber layer thickness by OCT Analysis (B scan) before and after surgery
- Outer segment photoreceptor thickness by OCT Analysis (B scan) before and after surgery
- Recurrence of EMM by OCT Analysis (B scan and C Scan)
- Operative report and the video recording area of EMM and ILM gripping (study of the correlation with the microsoctoma(s).

2.3 ANCILLARY STUDY

2.3.1 Ancillary study objective:

Compare primary and second endpoints of the principal study between patients with "spontaneous peeling" and patients with active peeling at 1, 6, 12 months.

2.3.2 Ancillary study endpoints:

- The main criterion : the difference between the number of microscotomas (sensitivity <10 dB) found before surgery and the number of microscotomas found at 6 months (number between 0 and 29).
- Visual acuity (VA) measured on the ETDRS scale and near vision (Parinaud) (inclusion visit, 1 month, 6 months and 12 months after surgery)
- Number and types of microscotomas by microperimetry (before and after surgery)
- Mean retinal sensitivity by microperimetry before and after surgery (at months 1, 6 and 12)
- Patient visual discomfort questionnaire: Symptoms and subjective improvement before and after surgery (at months 1, 6 and 12)
- Incidence of changes of the retinal nerve fiber layer SD by OCT Analysis (B scan and C Scan) before and after surgery.
- Sinusoid (IS/OS) line disruption by OCT Analysis (B scan and C Scan) before and after surgery
- Mean retinal thickness by OCT Analysis (B scan) before and after surgery
- Retinal nerve fiber layer thickness by OCT Analysis (B scan) before and after surgery
- Outer segment photoreceptor thickness by OCT Analysis (B scan) before and after surgery
- Recurrence of EMM by OCT Analysis (B scan and C Scan).

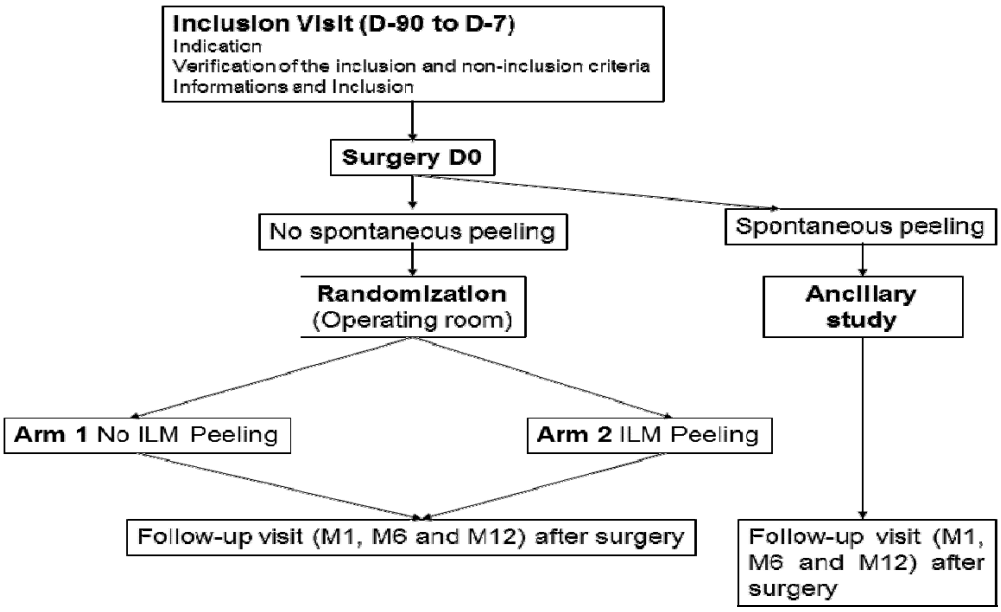
Study design

2.4 GENERAL METHODOLOGY OF THE STUDY

The research has the following characteristics:

- **Multicenter** and national study, between the seven national ophthalmology services of the CHU de Nantes, of the Hôpital Lariboisière,of the Hôpital Cochin , of the CHU de Dijon, of the Fondation Ophtalmologique Adolphe de Rothschild, of the Polyclinique de l'Atlantique de Saint-Herblain and of the Clinique Sourdille de Nantes,
- **Controlled** study
- Study **randomized and stratified by center**
- **Single-blind** study**,**
- **Prospective** study
- Study with **2 parallel groups**: "no peeling", "active peeling"
- Ancillary study about patients with spontaneous ILM peeling

2.5 STUDY DIAGRAM



3 STUDY POPULATION

3.1 DESCRIPTION OF THE POPULATION

EMMs are most often idiopathic, occurring in subjects over 60 years of age. They can more rarely be secondary to various diseases (diabetic retinopathy, inflammation (uveitis), trauma, recent eye surgery, retinal detachment or tear...).
Idiopathic EMMs are frequent and increase in incidence with age. They affect about 7% of patients after 50 years of age according to the Blue Mountains Eye Study (made on an Australian population) (20). They are often asymptomatic and not treated. In this study 28% of patients had a loss of visual acuity and 7.1% of metamorphopsia (distortion of lines). They then needed surgery.
The study population in our study concerns only patients with idiopathic EMMs, responsible for symptoms such as decreased visual acuity and metamorphopsia.
Recruitment is scheduled on 6 centers: the ophthalmology services of the CHU de Nantes (Prof. Michel Weber), of the Hôpital Lariboisière (Prof. Ramin Tadayoni), of the CHU de Dijon (Prof. Catherine Creuzot-Garcher) and of the Fondation Ophtalmologique Adolphe de Rotschild (Dr. Yannick Le Mer), of the Polyclinique de l'Atlantique de Saint-Herblain (Dr Julien Perol , Dr Alexandre Bourhis, Dr François Lignereux) and of the Clinique Sourdille de Nantes (Dr Frank Becquet) .
The number of subjects planned is 106 randomized patients (1 eye/patient), 53 patients randomized to the two groups in total.
People who participate in the research may not participate simultaneously in another research study during the study period (1 year).

3.2 INCLUSION CRITERIA

- Adult patients (>18 years old) female without childbearing potential or active contraception (intra-uterine device, contraceptive pill or contraceptive implant).
- Patients with an idiopathic symptomatic epimacular membrane; for patients with both eyes affected, the treated eye in the protocol will be the one that is most severely affected.
- Pseudophakic patients with transparent posterior capsule or open capsule or lensed patients with age-related cataracts
- Patients with social security
- Patients able to understand and follow the trial instructions
- Patients who have signed an informed consent

3.3 NON INCLUSION CRITERIA

- Patient with other retinal pathologies such as age-related macular degeneration ("AMD"), retinal vein occlusion, diabetic retinopathy, glaucoma with macular visual field defect
- Patients with uveitis or a history of uveitis
- Patients with any recent eye injuries or eye surgeries (<6 months)
- Patients participating in interventional clinical trial
- Pregnant or breast feeding women
- Vulnerable people: persons deprived of liberty; under trusteeship or under curatorship

STUDY TREATMENTS

3.4 AUTHORIZED, UNAUTHORIZED AND EMERGENCY TREATMENTS

3.4.1 Authorized treatments

All treatments are authorized.
In the postoperative phase: the standard treatment is a combination steroid and antibiotic eye drops (1 drop 3 times per day), duration 1 month.

3.4.2 Unauthorized treatments

No treatment is prohibited by the protocol.

3.4.3 Emergency Treatments

Emergency treatment will be those used in the practice of the different centers participating in the study and will not be codified.

4 STUDY PROGRESS

4.1 TESTS AND ANALYSIS

4.1.1 Detailed description of the parameters for evaluating efficacy

Detailed description of the parameters to assess effectiveness:

1/ Scale of evaluation of the ETDRS visual acuity: performed by an orthoptist (so as not to influence the patient's response, the orthoptist will not know what action has been carried out).

2/ Microperimetry

Microperimetry is a noninvasive test that allows a real-time, qualitative and quantitative assessment of visual function. Microperimetry is introduced in routine clinical diagnostic procedure which, with extreme precision, defines the retinal attachment point and the threshold of differential sensitivity of the retina. Retinal sensitivity is better within 3 degrees

around the fixing point, with a mean foveal threshold of 20 dB, and a 0.275 dB mean decrement for each decenie. Scotomas are defined as absolute (the patient does not receive the maximum stimulation, the sensitivity is 0 dB) or relative (reduction of retinal sensitivity compared to normal values is less than 10 dB). Assessing retinal function with this tool provides useful information both pathophysiologically and from a clinical point of view. These abnormalities could explain the hitherto non-assessable visual discomfort by conventional methods reported by some patients undergoing epimacular membrane and macular hole.
For all patients and to standardize the measurement, we use the "Ivana" protocol directed by the ophthalmology service of Lariboisière: a fixation target consisting of a red cross 2° in diameter, a white background monochromatic 4 asb, stimulus size Goldmann II with a projection time of 200 ms and a grid of 29 measurement points in the central 9° (centered on the fovea) with a 4-2-1 "double staircase" threshold strategy. Automatic "eye-tracking" will record eye movements throughout the exam. The standard operating procedure is in Appendix 9
In addition, we will conduct topographies of the macular area in specral OCT/SLO combined with microperimetry (OPKO/OTI, Miami, USA).

3/ Questionnaire "Patient discomfort": given to the patient for evaluation of symptoms (Appendix 7 and 8)

4/ SD OCT (Spectralis, Heildelberg, Germany):

The optical coherence tomography in spectral mode allows a precise anatomical pre- and postoperative analysis of the macula. The projected sequences include:

- RASTER (B scan): 1024 A-scans; 25 sections (9 frames) spaced by 240 µm, covering an area of 20° by 20°,
- FRONTAL acquisition (C scan): 512 A-scans; 193 sections (16 frames) spaced by 30 µm, covering an area of 20° by 20°.

On these sections, we will study:

- The retinal thickness at 1000 µm central and the fovean crown at 3000 µm, and the total macular volume,
- The presence of intra-retinal and/or subretinal edema,
- At the fovea level: analysis of internal trunk segments/outer segments of photoreceptors, integrity of the external limiting membrane, thickness of the layer of the outer section of the photoreceptors,
- In regard to microscotomas: thickness of the layer of ganglion cells at different times,
- The rate of anatomical abnormalities that are detectable from the layer of optical fibers in frontal "DONFL" and "SANFL",
- The EMM rate of recurrence

5) **Analysis of pre-and postoperative videos and photographs**

The EMM peeling procedure with or without ILM is filmed. A photo or screen shot of the video just after staining with Membraneblue-Dual® and a photo or a video screen shot at the end of ILM peeling will be made (depending on the blocks, certain devices enable video only videos while others are able to take both videos and photos).

The objective of the first picture is to visualize the spontaneous ILM peeling and scope. The purpose of the second photo is to see the surface of active ILM peeling. The advantage of video is that the gripping zone of the EMM and ILM can be viewed

Anonymous pre- and postoperative photos (according to the code defined in section 6.1.2.) will be sent to central Nantes, and examined by an ophthalmologist from Nantes to see the gripping areas of the EMM and ILM.

4.2 STUDY SCHEDULE

Between D-90 and D-7*:*

The **screening** visit includes:

- Patient information on the clinical trial
- Verification criteria for inclusion and non-inclusion
- Record history
- The signing of the informed consent form for participation
- The "patient discomfort" questionnaire (Appendix7)
- A measure of visual acuity with best optical correction after objective refraction, according to ETDRS scale, and near vision (Parinaud)
- An evaluation of the lens aspect at the slit lamp
- An examination of the fundus after pupillary dilation
- A review in SD OCT (Heildelberg)
- A microperimetry coupled to a SD OCT (Spectral OCT/SLO and microperimetry, OPKO/OTI, USA, MiamiHR SLO).
- Biomicroscopic examination of the anterior segment
- Retinophotography.

This visit can be split into 2 visits in the event of the absence of the investigator and/or the patient.

Day of surgery (D-0):

After injection of Membraneblue-Dual® specific to the study, a wait of 1 minute, then surplus extraction and washing of the vitreous cavity following the standard operating procedure set out in Appendix 5 and 6

Intraoperative picture to see the possible spontaneous ILM peeling.

If no spontaneous ILM peeling occurs, the patient will be randomized at the block.

Because the patient will undergo only local anesthesia during the surgery and in order to comply with the simple blind, the surgical team should not discuss the surgical procedure chosen in the operating block (so that the patient can not hear).

- Patients will be randomized into two groups
    - Group 1: "no peeling" where the ILM peeling will not be made
    - Group 2: "active peeling" where the ILM peeling is performed

At the end of the surgery, the retinal periphery will be checked, as usual after any vitreoretinal surgery. The operation will be filmed and the anonymous videos (depending on the code defined by section 7.1.2) will be centralized in Nantes to compare the appearance of microscotomas and grip areas of the EMM and ILM seen by video and photo

For about 30% of patients (21), the ILM peeling is done spontaneously. These patients will not be randomized but they can be included, if they want it, in the ancillary study. This ancillary study has the same follow-up visits (at 1, 6 and 12 months) with the same examinations as the principal study.

A report will be completed by the surgeon to validate the different operating times in the e-CRF, which will only be openly seen by the team.
The reporting procedure for the patient, and to maintain the single-blind, will just mention that the surgery was done following the protocol defined in the PEELING study. At the end of the study, patients will be informed of the results.

Always to avoid any bias, the follow-up visits will be made by an ophthalmologist or orthoptist who will not know what action has been carried out (blind team).

Follow-up visit M1 (1 month after the surgery ± 7 days)
*Examination: Visual acuity measured on the ETDRS scale, near vision (Parinaud), spectral domain optical coherence tomography (SD-OCT), Microscopic examination of the eye, microperimetry, fundus photography and post-operative “Patient discomfort” questionnaire (Appendix 8), Biomicroscopic examination of the anterior segment, retinal photography.
*AE

Follow-up visit M6 (6 months after the surgery ± 15 days)
*Examination: Visual acuity measured on the ETDRS scale, near vision (Parinaud), spectral domain optical coherence tomography (SD-OCT), Microscopic examination of the eye, microperimetry, fundus photography and post-operative “Patient discomfort” questionnaire (Appendix 8), Biomicroscopic examination of the anterior segment, retinal photography.
*AE
End of study visit M12 (12 months after the surgery ± 15 days)
*Examination: Visual acuity measured on the ETDRS scale, near vision (Parinaud), spectral domain optical coherence tomography (SD-OCT), Microscopic examination of the eye, microperimetry, fundus photography and post-operative “Patient discomfort” questionnaire (Appendix 8), Biomicroscopic examination of the anterior segment, retinal photography.
*AE

PEELING

STUDY SCHEDULE

Actions	Inclusion visit D-90 and D-7	D0 (Surgery)	M1 (30days±7days starting D0)	M6 (6 months ± 15 days starting D0)	M12 (12 months ± 15 days starting D0) End of study
Patient information	X				
Informed consent	X				
History (medications taken…)	X				
Randomization		X			
Surgery		X			
ETDRS visual acuity score and near vision (Parinaud)	X		X	X	X
Evaluation of the appearance of the lens at the slit lamp	X				
Biomicroscopic examination of the anterior segment	X		X	X	X
Fundus	X		X	X	X
SD OCT	X		X	X	X
OCT/SLO: microperimetry	X		X	X	X
Retinal photography	X		X	X	X
"Patient discomfort" questionnaire	X		X	X	X
Adverse events		X	X	X	X
2 Photographs		X			
Video		X			

4.3 IDENTIFICATION OF ALL DATA SOURCES NOT LISTED IN THE MEDICAL RECORD

Intraoperative data collected after the intervention: ILM surface spontaneously peeled, preemption point(s) of the EMM, preemption point(s) of the ILM, actively peeled surface of the ILM, pre and post-operative photos and operative video. All such data will be identified and coded by the coding described in paragraph 5.1.2.

4.4 SUBJECT DISCONTINUING RULES

4.4.1 Criteria for early discontinuing of a subject from the study

Withdrawal of consent,
Death of the patient,
Discontinuation of the study on decision of the sponsor,
Discontinuation of the study on decision of the investigator.

4.4.2 Procedures for early discontinuing of a subject from the study

The sponsor reserves the right to discontinue the study at any time for reasons that are well documented, especially in the case of unexpected adverse events that compromise the safety of patients included in this study.
Finally, if the recruitment rate is too low or in cases of non-compliance with Good Clinical Practice, the study may also be stopped prematurely.

4.4.3 Criteria for discontinuing part or all of the study (excluding biostatistical considerations)

The end of the study term corresponds to the participation of the last person that lends itself to the research.
The permanent or temporary cessation of the study may be decided by the CPC, the coordinating investigator or the University Hospital of Nantes.

5 DATA MANAGEMENT AND STATISTICAL ANALYSIS

5.1 STUDY DATA COLLECTION AND PROCESSING

5.1.1 Data collection

A case report form (CRF) will be created for each patient. All information required by the protocol must be provided in the CRF. It should include the data necessary to ensure compliance with the protocol and all data necessary for the statistical analysis, and identify major protocol deviations.

The people responsible for filling the CRF (investigator, CRA ...) should be defined and identified in the table of delegations of responsibilities of each center (kept in the investigator workbook).
Data collection will be done directly by the investigator or CRA in charge of the study, using an electronic CRF (eCRF) developed by the Promotion Department of the University Hospital of Nantes with Clinsignht (version of pack installed: 5.05.4102).

Each person (investigator, study coordinator, CRT, Project Manager, CRA) has a personal user account in connection with their role (profile) that has been assigned to them by the trial sponsor. The creation and administration of computer accounts are managed by the Data Manager in charge of the test.
Each user must change their initial password on first login, using an encrypted password of at least 8 alphanumeric characters, valid for 30 days. The system will revert to standby after 15 minutes of inactivity on the application, and users will be blocked after three unsuccessful login attempts.

An input and navigation guide will be provided to the investigator and TEC in charge of data collection. The Data Manager in charge of the trial will provide telephone support in case of problems related to the use of the Capture System application or eCRF.

This protocol will seee the formation of an open team and a blind team who will not have access to the same pages of the e-CRF.

5.1.2 Encoding data

By signing this protocol, the principal investigator and all co-investigators undertake to keep the identities of patients or patients who participated in the study confidential.

The first letter of the last name, the first letter of the first name and the inclusion number (code from the investigating center + patient number) will be the only information included in the case report form (CRF), which will enable the CRF to be matched to the patient later.

This code will be the only information included in the case report form (CRF), which will enable the CRF to be matched to the patient later.
The sponsor is also required to encode patient data on all documents that may be in his/her possession (reports from image studies, biological studies,...) that are attached to the CRF

5.1.3 Processing data

The collection of clinical data will be based on the establishment of a clinical database and the creation of input screens for image capture in accordance with the protocol and regulations currently in force.
The structure of the database and data entry screens will be approved by the sponsor of the trial.

5.1.4 Central processing of surgical videos

The surgery videos will be transferred anonymously according to the code described in paragraph 6.1.2, on USB keys provided by the sponsor.
A surgeon at the Department of Ophthalmology will note the gripping areas of the EMM in parallel with what the investigator has already noted.

5.2 STATISTICS

Name and contact details of the person in charge of the analysis: Christelle Volteau, statistician – Département Promotion Direction de la Recherche du CHU de Nantes. Statistical analysis will be conducted in SAS version 9.3.

A review of data will be conducted at the end of the study, prior to statistical analysis. This review will include the following parties: principal investigator, project manager, CRA monitoring, data-manager, statistician, and any person related to the protocol. The aim will be to review the progress of the study, potential problems and classify any minor or major deviations.

5.2.1 Description of planned statistical methods, including the planned intermediate analysis schedule

The variables measured at baseline are described for all patients in both groups by numbers and percentages for each category for categorical variables and the minimum, maximum, average, standard deviation and quartiles for the quantitative variables.

Analysis of the primary endpoint

The primary endpoint is the difference between the number of microscotomas measured before surgery and the number of microscotomas measured at 6 months (a number between 0 and 29).

The mean difference will be calculated in each of the two groups and compared using a mixed linear regression model to take into account the stratification of the randomization of the center (the center will be considered as a random effect) and ajustment for the preoperative number of microscotomas.

Then, centre effects will be analysed with a fixed-effect model.

Analysis of the secondary endpoints

- Comparison between the two groups of changes in the number of microscotomas between the preoperative visit and the visit at 12 months with a mixed linear regression model taking into account the stratification of the center (the center will be considered as a random effect).

- Description and comparison between the two groups of the types of microscotomas (relative or absolute) before surgery and at 1 month, 6 months and 12 months using mixed linear regression.

- Comparison between the two groups of changes in mean visual acuity between the preoperative visit and the visit at 12 months with a mixed linear regression model.

- Comparison between the two groups of changes in retinal sensitivity (average of the 29 points) between the inclusion visit and the visit at 12 months with a mixed linear regression model.

- Comparison between the two groups in the frequency of symptoms: blurred vision, metamorphopsia, relative scotoma, diplopia and micropsia at 1 month, 6 months and 12 months by stratified Chi-2 tests on the center.

- Description, for each group, of the number of miscroscotomas that are not located in a gripping area of the EMM and the ILM at 1 month and 6 months.

- Description, for each group, of the outcome (disappearance/persistence) of microscotomas that existed before the surgery at 1 and 6 months.

- Correlation between visual acuity and retinal sensitivity (the central point and the average of the five most central points), according to the measurement of Pearson or Spearman's correlation coefficients.

- Comparison of the percentage of abnormalities detectable by OCT in front of the layer of optical fibers at 1, 6 and 12 months, between the two groups, by stratified Chi-2 tests on the center. Description, in each group, of the territory where anomalies were found.

- Study of the association between the presence of abnormalities in the "SANFL" layer of optical fibers and the number of microscotomas at 1, 6 and 12 months by a mixed linear regression model.

- Comparison of the OCT B scan between the 2 groups using a generalized linear mixed model and linear regressions: overall retinal thickness of 1000 microns thickness of the central layer of the outer section of the photoreceptors at the foveal level, thickness of the cell layer (quantitative measures), integrity of the internal/external trunk segments of the photoreceptors at the foveal level, integrity of the external limiting membrane at the foveal level (qualitative measures: preserved line, discontinuous or absent), during the various visits.

- Study of the associations between data in the OCT B scan (described above) and visual acuity and between data in the OCT B scan and the presence of microscotomas at 1, 6 and 12 months using mixed linear regressions.

- Comparison of the percentage of recurrence of the EMM at 12 months between the two groups by a stratified Chi-2 test.

5.2.2 Statistical justification of number of inclusion

In a study by Tadayoni, assessing the ILM peeling in another pathology (senile macular hole) a number of microscotomas that was significantly higher in the active peeling group versus non-peeling group was found (p = 0.0093), with respectively 11.3 +/- 6.6 microscotomas in the active peeling group versus 2.9 +/- 4.6 in the non-peeling group (data to be published).

A retrospective study conducted in the Department of Ophthalmology of the University Hospital of Nantes in 2013 showed that of 11 patients who received active peeling, the number of microscotomas was 2.5 +/- 3.1 preoperatively and 6.5 +/- 7.3 at 1 month.

Based on the number of microscotomas found in the active peeling group in our retrospective study, with 80% power and a type I error of 5%, 100 patients are needed to highlight a halving of the number of microscotomas in the non-peeling group relative to the active peeling group (i.e. 6 +/- 6 microscotomas average peeling in the active group compared to 3 +/- 4.6 in the non-peeling group).
Usually, only very few patients do not attend their 6 month visit. However, the occurrence of EIGs (endophthalmitis, retinal detachment) may prevent the determination of the number of microscotomas at 6 months by microperimetry. Assuming that at most 5% of patients will be affected, 106 patients will be randomized, or 53 patients per group.

As up to 52.1% of patients have a spontaneous peeling and will be out of the study, in order to have 106 patients randomized, 222 patients will be enrolled in the study.

The six centers' ability to recruit is estimated to be 120 patients per year (30 patients per center), given that the primitive EMM is a common disease.

5.2.3 Ancillary study's statistics

For about 52.1% of patients (21), the ILM peeling is done spontaneously which corresponds to about 116 patients . These patients will be compared to the active peeling patients group.

The endpoints are :

- The main criterion : the difference between the number of microscotomas (sensitivity <10 dB) found before surgery and the number of microscotomas found at 6 months (number between 0 and 29).
- Visual acuity (VA) measured on the ETDRS scale and near vision (Parinaud) (inclusion visit, 1 month, 6 months and 12 months after surgery)
- Number and types of microscotomas by microperimetry (before and after surgery)
- Mean retinal sensitivity by microperimetry before and after surgery (at months 1, 6 and 12)
- Patient visual discomfort questionnaire: Symptoms and subjective improvement before and after surgery (at months 1, 6 and 12)
- Incidence of changes of the retinal nerve fiber layer SD by OCT Analysis (B scan and C Scan) before and after surgery.
- Sinusoid (IS/OS) line disruption by OCT Analysis (B scan and C Scan) before and after surgery
- Mean retinal thickness by OCT Analysis (B scan) before and after surgery
- Retinal nerve fiber layer thickness by OCT Analysis (B scan) before and after surgery
- Outer segment photoreceptor thickness by OCT Analysis (B scan) before and after surgery
- Recurrence of EMM by OCT Analysis (B scan and C Scan).

Mixed linear regressions models and stratified Chi-2 test will be used for comparisons.

5.2.4 Expected level of statistical significance

The level of statistical significance was set at 0.05.

5.2.5 Consideration method for missing, unused or invalid data

Primary endpoint : very few patients generally refuse to attend the visit at 6 months. However, in case of no show or of EIG (endophthalmitis, including retinal detachment), missing values will be dealt with multiple imputation.

Secondary endpoints : there will be no attribution of missing data for the secondary endpoints.

5.2.6 Managing changes made to the initial analytical strategy

A statistical analysis plan will be prepared before freezing the database and will detail any changes to the statistical section of the protocol.

5.2.7 Choice of subjects to include in analysis

The primary analysis population is the population "Intend to Treat". This population consists of all patients randomized into the study.

A sensitivity analysis on the "Per protocol" population will be achieved. This population includes patients who are the most respectful of protocol: compliance with inclusion and non-inclusion criteria, no major protocol deviations and availability of the primary endpoint.

5.2.8 Randomization

Randomization is open and stratified by center. It will be performed by blocks according to a 1:1 ratio.

Randomization will be done via the Clinsight software by connecting to the website: **https://www.dirc-hugo-online.org/csonline/**. Connection will be made with a login, a password and a study number (DIRCXXX) issued by a data-manager from the Department Promotion of Research at the CHU de Nantes.

The following information must be provided:

- First letter of the last name
- First letter of the first name
- Birth date
- Compliance with the criteria for inclusion and non-inclusion (yes/no)
- Signed consent (yes/no)
- Spontaneous peeling (yes/no) – only "no" allows for randomization.

After injection of the Membraneblue-Dual® according to protocol, in order to view the possible spontaneous ILM peeling, and if there is no spontaneous ILM peeling, the patient will be randomized at the block.

The number and the arm of randomization will be automatically assigned to the investigator at the time of randomization. A confirmation email will be sent to the person who performed the randomization and to all concerned and will be open in this study.

The randomization list will be conducted by a statistician from the Research Promotion Department of the University Hospital of Nantes. An explanatory guide to randomization will be available online in Clinsight.

6 SAFETY

6.1 DEFINITIONS

6.1.1 Adverse Events (AEs)

An AE is any untoward medical occurrence in a patient or study subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

All the AEs encountered during the study, which are noticed by the investigator or reported by the subject, should be documented in the Adverse Event section of the CRF.

The severity (i.e. intensity) of all AEs will be graded:
1 = mild
2 = moderate
3 = severe
4 = life-threatening

6.1.2 Serious Adverse Events (SAEs)

Any adverse event that:

- results in death
- is life-threatening
- requires hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- leads to a congenital anomaly or birth defect
- is an important medical event that may jeopardize the patient or may require medical intervention to prevent any of the criteria listed above or/and are listed on IME list

6.2 SAFETY EVALUATION PARAMETERS

Non-applicable

6.3 LIST OF THE MOST FREQUENT EXPECTED AE

Under this protocol:

6.3.1 Expected AEs resulting from epiretinal membrane and cataract surgery *(according to the Société Française d'Ophtalmologie, www.sfo.asso.fr)* are:

- endophthalmitis (eye infection) (1-3 in 1000),
- changes in the macula, tear(s) of the retina, retinal detachment (3%) that may occur after surgery and require additional treatment by reoperation and/or laser,
- clouding of the cornea,
- central retinal edema,
- retinal burn from the illumination of the surgical microscope,
- inadequately sealed scar,
- partial collapse of the upper eyelid,
- subconjunctival hemorrhage or of eyelid,
- perception of floaters,
- increased sensitivity to light,
- inflammation of the eye,
- increased intra-ocular pressure,
-

6.3.2 Expected AEs resulting from other concomitant treatments (e.g. analgesic drugs, postoperative treatment: steroid and antibiotic eye drops):

These treatments are used according to the product information for the CE-marked Medical Device, or according to the Summary of product characteristic of each drugs.

6.4 MANAGEMENT OF ADVERSE EVENTS

6.4.1 AE/SAE reporting

All SAEs whether expected or unexpected, require the completion of a SAE report. The investigator should verify that all the information noted in this report is precise and clear (no abbreviation, *etc.*).
All the surgery-related adverse events occur inside the operating room must be reported in the e-CRF and, if they meet a seriousness criterion, transmitted to the Sponsor;
Because they could be a risk of adverse drug reaction, any inadequacy or malfunction of a medical device or surgical equipment has to be notified to the sponsor as well as any misuse or error.

In this protocole, the SAE that will not require a report to the sponsor are:
-those linked to patient medical history as expected usual evolution, conventional treatment or previously planned intervention.
-hospitalisation or length of hospital stay due to social or technical factors
SAEs should be reported immediately (within 24 hours of the investigator becoming aware of the event) to the sponsor by fax (Research Department, CHU de Nantes – Fax number: +33 2 53 48 28 36).
On receipt of an unexpected SAE report, the sponsor should report it to the regulatory authorities. Once a year, the sponsor draws up an annual safety report.

6.5 FOLLOW-UP PROCEDURE AND PERIOD FOR SUBJECTS FOLLOWING ADVERSE EVENTS

In the event of SAEs involving discontinuing from the study or SAEs ongoing at the end of the study, the patient should be subject to follow-up until the SAE is resolved.

7 ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

7.1 PERMISSIONS TO ACCESS DATA AND SOURCE DOCUMENTS

The medical data for each patient will only be sent to the sponsor or persons authorized by the sponsor and to competent health authorities (if applicable), subject to terms guaranteeing their confidentiality.

The sponsor and the regulatory authorities may request direct access to medical records for the purposes of verification of the procedures and/or data of the study, without breaching their confidentiality and to the extent permitted by applicable laws and regulations.
Data collected during the study will be processed electronically in compliance with the requirements of the CNIL (compliance with the French Reference Methodology MR001).

7.2 MONITORING

The monitoring will be provided by the Department of Promotion Research. A Clinical Research Associate (CRA) will visit each site to perform a quality control of the data reported in the CRFs.

The monitoring plan is defined through consultation between the research team and the lead institution in the objectives of the study, according to an internal procedure at the DPRC.

During these visits, the CRA will review study plan compliance, adherence to the protocol, and data quality. The CRA will compare CRFs and ensure that the study is being conducted in compliance with pertinent regulatory requirements.

The investigator will provide the CRA with direct access to CRFs and to the subject's records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification, as well as to any other study documents.

7.3 INSPECTION/AUDIT

As part of this study, an inspection or audit may take place.

7.4 ETHICAL CONSIDERATIONS

7.4.1 Informing the patient

The investigator agrees to provide the subject with clear and precise information about the protocol and request him/her for written informed consent (information form and consent form appended). The investigator will give the subject a copy of the information form and consent form. The subject can only be enrolled in the study after reading the information form and signing and dating the consent form. If this is not possible, a third party (independent from the study) proves the subject's consent. The investigator should also sign and date the consent form. Both documents should be issued at least in duplicate hard copy format so that the patient and the investigator can each keep a copy. The investigator's original will be placed in the investigator's file.

7.4.2 Ethical Review Board

The head of research undertakes to submit the study to the prior authorization of a Ethics Committee (CPP). The information provided concerns on the one hand the terms and nature of the research and the safeguards for patients in this trial on the other.

7.5 AMENDMENTS TO THE PROTOCOL

Requests for substantial modifications should be addressed by the sponsor for approval or notification to ANSM and/or the Ethical Review Board concerned in compliance with the law 2004-806 of August 9, 2004 and its implementing decrees.

The amended protocol should be a dated updated version. If necessary, the information form and consent form should be amended.

7.6 REGISTRATION WITH THE COMPETENT AUTHORITIES

For this protocol, a request will be addressed to the ANSM for approval.

7.7 STUDY FUNDING AND INSURANCE

The sponsor shall fund the study and take out an insurance policy covering the financial consequences of civil liability in compliance with the regulations.

7.8 PUBLICATION RULES

A copy of the publication will be delivered to the CHU de Nantes, the study sponsor, which will necessarily be mentioned. The authors will be determined in proportion to the number of subjects enrolled. The coordinator shall draw up the list of authors.

LIST OF APPENDICES

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- Appendix 7 : Pre-operative Questionnaire "Patient discomfort"
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APPENDIX 1: INVESTIGATOR LIST

Name, First name	Title	Area of medicine / Role	Position in the study	Name and address of the institution and department	Phone number, fax number and email	RPPS No.
Weber, Michel	Pr	ophthalmologist	Coordinator investigator	CHU de Nantes Place Alexis Ricordeau 44 0+93 Nantes cedex 1	Phone number : 0661180456 Email : michel.weber@chu-nantes.fr	10003824900
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