NEAR INFRARED LIGHT PHOTOBIOMODULATION TREATMENT FOR DIABETIC MACULAR OEDEMA (NIRD TRIAL)

PROTOCOL

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INVESTIGATOR SIGNATURE PAGE

I agree to:

Implement and conduct this study diligently and in compliance with the protocol, good clinical practices and all applicable laws and regulations.

I have read this protocol and I agree to all aspects.

Investigator Printed Name	Signature	Date
Investigator Printed Name	Signature	Date
Investigator Printed Name	Signature	Date
Investigator Printed Name	Signature	Date

Abbreviations of definitions and terms:

AE	Adverse Event
anti-VEGF	anti Vascular Endothelial Growth Factor
BP	Systemic Blood Pressure
BCVA	Best Corrected Visual Acuity
CF	Colour Fundus photography
CRF	Case Report Form
DMO	Diabetic Macula Oedema
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
FFA	Fundus Fluorescein Angiography
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
NIR	Near-infra Red
OCT	Optical Coherence Tomography
SAE	Serious Adverse Event
SD-OCT	Spectral Domain Optical Coherence Tomography
TGA	Therapeutic Goods Administration
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor

1 Synopsis of Near InfraRed laser for Diabetic Macular Oedema (NIRD) Study

1.1 Background:

Near-infrared light (NIR) at power densities a hundred times lower than conventional thermal treatments have been shown in animal models to promote the healing of injured cells, including blood vessels and neurons in the retina. The Macular Research Group's laboratory research unit has shown that NIR laser reduces vascular leak that occurs after Muller cell ablation in their transgenic model

1.2 Hypothesis:

That treatment with NIR light reduces diabetic macular oedema by exerting a positive beneficial effect at the retinal cellular level

1.3 Trial design:

Patients with diabetic macular oedema in one eye as defined by the eligibility criteria will receive thrice weekly 90 second treatments with NIR laser, supplied by Ellex, for 4 weeks. Twenty one patients will be sequentially allocated into three groups to receive laser doses 25, 100 or 200 mW/cm^2. The central 1 mm will be shielded so that the fovea will be protected in the event of any unanticipated toxic effect on the retina.

1.3.1 Primary outcome:

- Reduction in central macular thickness measured by optical coherence tomography at the conclusion of treatment and at 8 weeks compared with baseline.

1.3.2 Secondary outcomes:

- LogMAR Best Corrected Visual Acuity (BCVA)
- Time to oedema reduction
- Time to oedema recurrence
- FFA assessment of leak and capillary closure before (at baseline) and after intervention (week 5 and 16)
- Change in retinal sensitivity (dB) as measured by microperimetry from Baseline to Week 1, Week 5, Week 16 and 6 month follow up visit.

1.4 Power calculation:

This study is an exploratory study designed to provide estimates of outcomes for future studies, therefore power calculations have not been applied. Seven patients per group will be sufficient to produce these estimates and will give an indication of the effective dose range

1.5 Significance:

This study will shed light on whether a novel treatment that may complement existing treatments is safe and whether it warrants further investigation in a larger study

2 Research Plan

2.1 Background

Diabetic retinopathy is a common cause of severe loss of vision and the most common cause of blindness in individuals between the ages of 20 and 65 years in developed countries. Swelling of the central retina, or “macular oedema”, is the commonest cause of visual loss in diabetic retinopathy.

Diabetic macular oedema (DMO) has in the past been treated with continuous wave thermal laser photocoagulation to areas of leak in the macula according to established guidelines which take into account the extent of the leak and its proximity to the centre of the macula, the “fovea”. This treatment does not usually improve vision and causes some permanent tissue damage. More recently injections into the eye of drugs such as vascular endothelial growth factor (VEGF) inhibitors or glucocorticoids have become first line treatment for DMO, but these have to be given regularly, they are expensive and they carry a small risk of serious adverse events.

Near-infrared light (NIR) at power densities a hundred times lower than conventional thermal treatments have been shown in animal models to promote the healing of injured cells, including blood vessels and neurons in the retina. Studies claim that NIR treatment augments cellular energy metabolism, enhances mitochondrial function, increases cytochrome C oxidase activity, stimulates antioxidant protective pathways and promotes cell survival.

The major foundation for this work comes from the Macula Research Group’s laboratory studies of the role of metabolic dysfunction in retinal disease.

Mitochondria are an essential component of energy metabolism. They house the cellular machinery for the tricarboxylic acid cycle and oxidative phosphorylation, which together convert pyruvate, produced by the glycolytic pathway, to ATP. Both photoreceptors and “Müller cells”, which are specialized glial cells, contain abundant mitochondria [1]. Müller cells contain mitochondria throughout their length [2]. This enrichment with mitochondria is consistent with the high energy demand of photoreceptors and the high metabolic activity of Müller cells**.** A potential role of mitochondrial bio-energetic deficits coupled with increased mitochondrial oxidative stress has been observed in neurodegenerative conditions [3].

There is evidence that 670nm Near Infra Red light activates cytochrome c oxidase, a key constituent of the mitochondrial electron transport chain, which subsequently results in increased electron transfer and improved mitochondrial respiration and ATP synthesis [4]. Near Infra Red treatment has recently been reported to attenuate neuronal damage in animal models of retinal degenerations [5,6]. It is believed that Near Infra Red treatment regulates mitochondrial function through increasing mitochondrial membrane potentials for ATP production, thus inhibiting neuronal apoptosis and neuroinflammation and improving glial-neuronal interactions [5, 6-8].

Our preliminary studies on a mouse model of retinal vascular leak caused by selective ablation of Muller cells suggest that Near Infra Red treatment not only protected photoreceptors but also reduced vascular leakage after induced Muller cell disruption. (Figure)

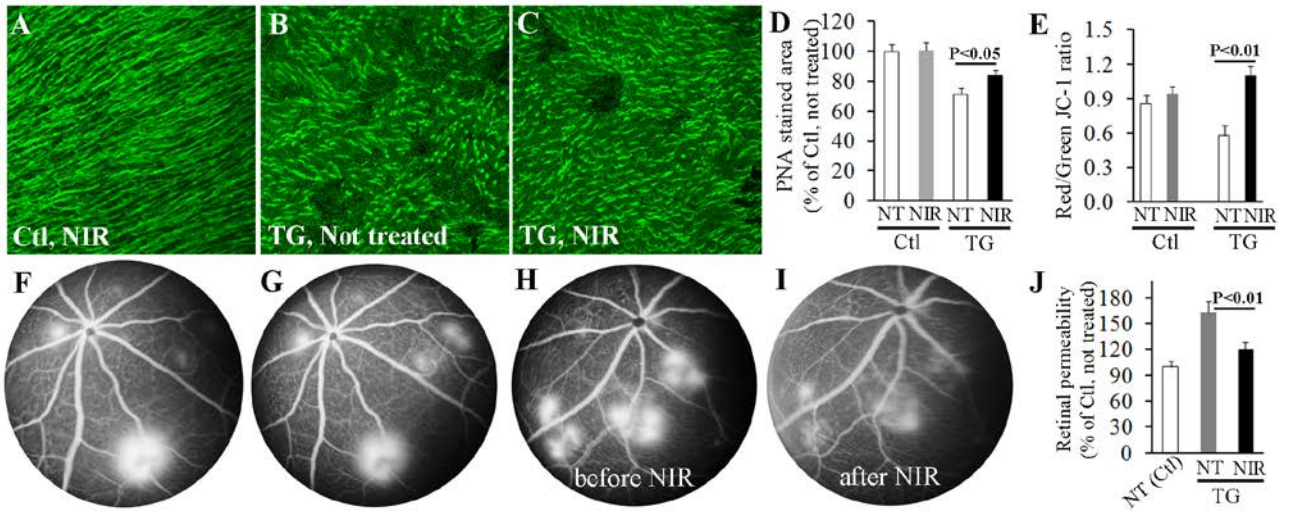


Figure. (A-D), Near Infra Red (NIR) treatment did not affect photoreceptors in control (Ctl) mice but protected photoreceptors from injury in Muller cell KO (TG) mice, in which treatment was initiated from immediately after induced Muller cell ablation. (D), peanut-agglutinin (PNA)-stained cone outer segments as shown in (A-C) were quantified by image analysis. (E), evaluation of mitochondrial membrane potentials at the level of photoreceptor inner segments suggested that NIR treatment improved the function of photoreceptor mitochondria. Retinal wholemounts were stained using the JC-1 mitochondrial dye. A shift of the light emission from 525nm (green) toward 590nm (red) indicates increased mitochondrial membrane potentials [9]. (F-J), NIR treatment reduced established retinal vascular leakage. (F, H), fluorescein angiography was performed to confirm vascular lesions in TG mice 3 months after Müller cell ablation. (G), angiogram of an untreated eye in (F). (I), angiogram of the eye in (H) after 9 days of NIR treatment. (J), quantitative analysis of retinal permeability to FITC-dextra indicates that NIR treatment significantly inhibited retinal vascular leakage. N=12~20/group in (D, E and J). NT=Not Treated.

A pilot study completed at the Stokes Veteran Affairs Hospital required patients with non-centre involving diabetic macular oedema to self administer the NIR treatment twice a day for 160 seconds for 2 months achieved a mean reduction in macular thickness of 20%.[10]

Clinical trials of NIR laser treatment for centre involving diabetic macular oedema (see clinicaltrials.gov #NCT00846092 for a study in Wisconsin) have started but no well-conducted study has reported its' results yet

The NIRD Trial described here improves on the Wisconsin Study and the Stokes Study (in which the patients administered the treatment themselves at home using an NIR light emitting diode (LED) [10] through the use of a slit lamp biomicroscope mounted NIR laser generated light source to be administered to the patient in a consulting clinic. This ensures that the amount of treatment is delivered at an accurate predetermined dose only to the part of the retina where it is required.

Review of safety post enrolment of the first cohort in the NIRD study has shown the NIR light to be safe. Results also indicate that a delayed beneficial effect may be present post completion of NIR treatment.

2.2 Objective

This will be a 1 month exploratory study, with outcome measures assessments at 8 weeks and further assessment visit as 12 and 16 weeks, followed by a 6 month safety visit.

The specific aim of the study is to test the following hypothesis:

- That treatment with NIR light reduces diabetic macular oedema

Outcomes
Variables related to the progression or resolution of diabetic macular oedema will be serially examined in the study eye of all patients to determine the effects of NIR treatment. These are:

2.2.1 Primary Outcome Measure at 8 weeks

Reduction in central macular thickness and total macular volume as measured by Spectral Domain Optical Coherence Tomography (OCT)

2.2.2 Secondary Outcome measures at 1month, 8 weeks, 12 weeks and 16 weeks

- Best corrected LogMAR Visual Acuity (VA)
- Time to oedema reduction
- Time to oedema recurrence
- FFA assessment of leak and area of ischemia before and after intervention
- Change in retinal sensitivity (dB) as measured by microperimetry from Baseline to Week 5, 8, Week 16 and 6 month visit.

2.2.3 Safety outcomes will be:

- Any loss of VA
- Any increase in macular thickness as measured by OCT

3 Design

A cohort of 21 patients satisfying the inclusion criteria will be recruited from the outpatient hospital clinic. They will be sequentially allocated into one of three groups. Each group will have seven patients with group 1 enrolment completed first, followed by group 2 and finally, group 3. Each group will be managed identically but will receive a different dose of NIR energy.

Group 1 will be treated with a dose of 25 mW/cm2 for 90 seconds (now fully enrolled)
Group 2 will be treated with a dose of 100 mW/cm2 for 90 seconds (now fully enrolled)
Group 3 will be treated with a dose of 200 mW/cm2 for 90 seconds.

3.1 Quality Assurance

Standardised protocols have been developed for NIR laser light treatment, refraction, fluorescein angiography, microperimetry, measurement of best-corrected visual acuity, OCT measured subfield volume and thickness.
The major quality assurance features of the study are:

- Standardised eligibility and exclusion criteria
- Adherence to treatment protocol and follow-up schedule
- Trained BCVA and imaging technicians
- Monthly meetings of personnel to review methods and discuss problems

3.2 Organisational Structure of the Study Group

The centre will have trained BCVA examiners, a study coordinator, a photographer, an ophthalmologist performing the NIR laser light delivery, and an optical coherence tomography (OCT) examiner. There will be no masking in this study.

4 Participant Eligibility

4.1 Patient Consent

The study requires that written informed consent is obtained from each participant prior to their enrolment in the study. The participant will be asked to sign the consent form only after an investigator has explained the purpose of the study and the participant has had time to read and understand the information sheet.

With the consent of the participant, it is the Investigator's responsibility to notify the primary care physician of the participant's participation in the study, provided that such a physician can be identified for the participant. A letter will be sent to the physician stating the nature of the study. A copy shall be retained by the study site.

4.2 Eligibility of Participants into the Study

4.2.1 Inclusion Criteria

a) Diabetic Macular Oedema with centre involving thickness of >300μm
b) Age >= 18 years
c) Diagnosis of diabetes mellitus
d) Best corrected visual acuity of 6/9 to 6/60 (letters 77- 33)
e) Intraocular pressure 6 to 25 mmHg
f) Written informed consent has been obtained.

4.2.2 Exclusion Criteria

a) Known allergy to agents used in the study e.g. fluorescein
b) Women who are pregnant, nursing, or planning a pregnancy, or who are of childbearing potential and not using reliable means of contraception. A woman is considered of childbearing potential unless she is postmenopausal and without menses for 12 months or is surgically sterilised
c) Loss of vision due to other causes (e.g. age related macular degeneration, myopic macular degeneration, retinal vein occlusion)
d) Macular oedema due to other causes
e) An ocular condition that would prevent visual acuity improvement despite resolution of oedema (such as foveal atrophy or substantial premacular fibrosis)
f) Treatment with intravitreal triamcinolone acetonide (IVTA) within the last 6 months or peribulbar triamcinolone within the last 3 months, or anti vascular endothelial growth factor (VEGF) drugs: ranibizumab and aflibercept, within the last 2 months.
g) Cataract surgery within the last 3 months
h) Retinal laser treatment within the last 4 months
i) Media opacity including cataract that already precludes adequate macular photography or cataract that is likely to require surgery within 6 months

j) Intercurrent severe disease such as septicaemia, any condition which would affect follow-up or photographic documentation (e.g. geographical, psycho-social)
k) History of chronic renal failure requiring dialysis or renal transplant
l) Blood pressure >180/100
m) Patient has a condition or is in a situation that in the investigator's opinion may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study

4.3 Bilateral/Fellow Eye Enrolment

If both participants' eyes are eligible for the study, only the eye with the worse DMO will be enrolled.

5 Entry into the Study

5.1 Patient Orientation

At the initial visit, patients are examined to determine whether they are eligible for the study and if so the study is discussed with them. They are informed of the possible risks and benefits of the study treatment. The patient's likely eligibility is assessed. The patient either reads the detailed informed consent or it is read to them and the patient is given time to study the patient information sheet. Any questions related to the study will be answered. The patient is allowed some time to consider the study prior to the consent form being signed.

5.2 Baseline Examination (Screening Visit)

If the patient is willing and has agreed to participate in the study then a complete baseline examination is conducted (does not need to be the same day as the signing of the consent) which includes the following

a) Visual Acuity. Best corrected visual acuity will be assessed on LogMAR chart
b) Intraocular Pressure (IOP) measurement
c) Slit lamp examination for grading of lens opacities
SD OCT: High definition Spectral domainVolume Scan or Macula Cube
Cross Hair scan or HD 5-line raster

d) Fundus photography and fluorescein angiography. See Section 12 for photography and angiography details.
e) Fundus autofluorescence. See Section 13.1
f) Urine pregnancy test (for women of child bearing potential only)
g) Blood pressure
h) Assessment of concomitant medications and medical history
i) Visual function as assessed by Microperimetry

Full baseline assessment will be performed on the Tuesday or Friday on the week immediately prior to starting NIR treatment. If clinics/staff are not available for baseline assessment on Tuesday or Friday, another day in the week immediately prior to starting NIR treatment may be selected, however the remaining treatment and visit schedule must be adhered to according to the protocol.

5.3 Day 1

Once the patient has met all of the eligibility criteria they will return for the Day 1 visit which will occur on the Wednesday the week after screening. The following procedures will occur at this visit:

a) AE and Conmed history
b) Microperimetry
c) Dilation of study eye
d) Confirmation of eligibility
e) NIR light treatment

6 NIR Light Treatment

NIR light treatment will commence on the Wednesday of the next week after the baseline visit.

The procedure will be performed whilst the participant is seated at a slit lamp according to the set protocol:

The patient will be seated at the slit lamp laser delivery system and after the eye has been dilated and anesthetised with topical eye drops a standard fundus contact lens (area centralis) will be placed on the eye through which the posterior pole will be visualised while the treatment is delivered.

Each NIR light treatment will consist of a 90 second exposure of the macula of the study eye to the ELLEX Integre NIR laser with the patient fixating on the central aiming beam. The laser light beam is 4.5mm in diameter with a central masked area of 1.0 mm diameter containing the central fixation target. In this way the central macula will be spared in the event of an adverse effect of the laser, which we do not anticipate.

6.1 Treatment Week 1

Treatment 1 will be applied on Wednesday and Treatment 2 on Friday.

6.2 Treatment Weeks 2-4

Treatments 2 to 11 will be applied on the Monday, Wednesday and Friday of each subsequent week for 3 weeks.

6.3 Treatment Week 5

On week 5 patients will have their final laser treatment (12) on Monday and will be assessed on the Tuesday.

The investigator can use clinical discretion to determine if the patient would not benefit from receiving further treatment at any time point during the treatment schedule or if any adverse events appear to occur.

6.4 Rescue Treatment & Standard of Care

Patients with an increase of 100 microns in central macular thickness on OCT or a significant loss of vision (defined as a loss of 10 or more letters [2 lines] on a vision chart) at any stage in the study will

be discontinued from the study treatment and treated as per standard of care. Patients who are discontinued from the study and are treated with the standard of care during the study period will continue to be followed for the safety at the specified time points.

At the 16 week visit, patients will be assessed for the need for standard of care therapy according to each investigator's usual practice.

6.5 Assessments

VA and OCT will be performed on the Friday of each treatment week.

The full final assessment will be performed on Tuesday following Treatment 12.

7 Patient Visits and Examination

7.1 Introduction

Patients will be assessed with respect to safety outcomes for which standardised procedures have been developed:

- BCVA/VA by a trained technician will be undertaken.
- Adverse events assessment
- Concomitant Procedure assessment
- Dilated fundal examination
- Grading of cataract and anterior and posterior chamber cells
- Macular thickness by optical coherence tomography (OCT)
- Visual function as assessed by Microperimetry

Refer to the Schedule of Visits table in Section 15 regarding the timing for each of these assessments

7.2 Patient follow-up

Patients will be seen for treatment visits according to Section 6 above and then for an assessment visit at week 8.

The schedule of visits table in Section 15 outlines the timing for each of the required assessments.

Any patient missing an appointment will be contacted within 1 day to establish their status and another appointment will be made immediately.

In the event that a patient withdraws from the study, an early exit visit should be conducted where possible.

7.2.1 Safety follow-up visit

There is a safety follow-up visit 6 months after the last administration of study laser treatment. If a patient has withdrawn early from the study they will still be asked to attend these visits.

7.3 Treatment of Adverse events

7.3.1 Introduction

Adverse Event Definition: Any undesirable clinical occurrence in a subject whether it is considered to be device related or not, that includes a clinical sign, symptom or condition and/or an observation of an unintended technical performance or performance outcome of the device.

Examples of an AE **include**:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational treatment administration.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of a concurrent medication (overdose per se should not be reported as an AE/SAE).

This trial is being carried out in the facilities of quaternary ophthalmic referral centre with extensive experience in laser therapy. The medical staff are well experienced in dealing with all adverse events associated with laser therapy.

Adverse events will be collected from the first NIR laser treatment visit, not necessarily from the date of consent in the event that the patient is not treated on the same day as they are consented. The incidence of adverse events will otherwise be recorded throughout the duration of the study and at the safety follow up visit. These will be graded by the Principal Investigator as mild, moderate or severe.

Serious Adverse Event Definition: Any untoward medical occurrence that:

- results in death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect

For SAE's the relationship to study treatment will be graded as related, unrelated, probable, unlikely or likely. SAE's will also be graded as expected or unexpected

Serious adverse events (SAE's) as defined by the International Conference on Harmonisation, Good Clinical Practice (ICH-GCP) as per above will be reported as SAE's to the approving HREC according to local requirements.

The following events are to be considered adverse events but not serious adverse events and therefore reporting as SAE's is not required:

- Hospitalizations for elective surgery
- Hospitalizations for admissions of less than 24 hours in duration
- Hospitalizations to the emergency department not requiring admission within the hospital
- Care delivered as "hospital in the home" or similar in home service (unless other SAE criteria are met such as persistent disability)

Pregnancies are not considered AE's or SAE's, however pregnancies in female study patients will be recorded in the study data.

7.3.2 Management of diabetes

The risk factors for diabetic retinopathy will be discussed with all participants at baseline and reviewed from time to time throughout the study. All participants will be informed that optimal control of blood glucose and blood pressure reduces the risk of loss of vision. Investigators will ensure that adequate arrangements are in place for the medical management of participants' diabetes, and will correspond in writing with the care providers at least at the baseline and closeout visits.

7.3.3 Recording AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostic reports) relative to the event. The investigator/site staff will then record all relevant information regarding an AE/SAE in to the eCRF. Any SAE documentation forwarded to TGA/HREC will be de-identified maintaining patient anonymity. For each adverse event, start and stop dates, action taken, outcome, intensity (see Section 7.3.1) and relationship to study treatment and causality must be documented.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In the absence of a diagnosis, the individual signs/symptoms should be documented.

8 Endpoints

8.1 Primary and Secondary Outcomes

Primary outcome:

- Reduction in high definition Spectral Domain Heidelberg Optical Coherence Tomography (OCT) subfield volume measurements at 8 weeks.

Secondary outcomes at 1 and 2 months:

- LogMAR VA
- Time to fluid reduction
- Time to oedema recurrence
- FFA assessment of leak and capillary closure before (at baseline) and after intervention (Week 5 and 16)
- Change in retinal sensitivity (dB) as measured by microperimetry from Baseline to week 1, week 5, week 8 and Week 16

Safety outcomes will be:

- Any loss of BCVA/VA
- Any increase in any OCT subfield

9 Statistical aspects of the study, safety and reporting

9.1 Time Limits for Completing Study Visits

Due to the intensity of the visit schedule all patients will be selected based on their ability to maintain the intensive laser light therapy regimen. Should a laser visit be scheduled on a day which falls on a public holiday or similar all care should be made for the treatment visit to be administered on a day immediately before or after the scheduled treatment day taking into account weekends. All patients should be seen within two weeks of the safety follow up visits.

9.2 Statistical Analysis of OCT measurements

Retinal thickness measurements will be checked for artefacts. Only scans where the software was able to pick up the retinal thickness between the internal limiting membrane and the retinal pigment epithelium will be used.

The principal measurement of macular thickness will be the reading that appears in the central circle. Absolute change and percentage change in “abnormal thickness” will also be analysed in each subfield.

OCT measurements will be made and entered into the database.

9.3 Safety monitoring

The incidence of adverse events will be recorded throughout the duration of the study and at the safety follow up visits. The trial will be stopped if there is a significant (P = 0.01) incidence of severe adverse events or any event arises which renders continuation of the study not to be in the interests of participants.

9.4 Electronic Case Report Form (eCRF)

An electronic case report from will be completed for each patient for each study visit summarising all of the screening and study data. Patients will be referred to by their study identification code only to retain confidentiality within the database.

10 Investigational Equipment

10.1 Description

The Ellex Integre NIR Laser is a slit lamp microscope mounted 670nm light source that can be varied in brightness by the operator to set the required power density from 50 to 500 mw per square centimetre. This level is between 1x and 10x the brightness of the NIR LED device used in the Wisconsin Study but even at the highest level of intensity is only just comparable to the energy density of the aiming laser used in a standard thermal laser photocoagulator. At its highest brightness this is 50X lower in energy density than a photocoagulator. As an additional safety measure the Ellex Integre NIR laser beam is 4.5mm in diameter with a central masked area of 1.0 mm diameter in order to avoid illuminating the central macula with light.

The Ellex Integre NIR Laser system has a user selectable exposure duration control permitting the user to preset the treatment time duration.

10.2 Maintenance of Machine/Equipment

The Ellex Integre NIR laser equipment will be installed and calibrated at the start of the trial and inspected and tested for accurate calibration at least annually for the duration of the trial.

11 Administration Procedures

11.1 Ethical Considerations

Information on the ELLEX Integre laser is summarised in Section 10

This study will be carried out according to the Declaration of Helsinki, the NHMRC National Statement on Ethical Conduct in Research Involving Humans (2007) and the Notes for Guidance on Good Clinical Practice as adopted by the Australian Therapeutic Goods Administration (2000) (CPMP/ICH/135/95) and the ICH GCP Guidelines.

11.2 Human Research Ethics Committee

The Protocol will be submitted for approval to the site's Human Research Ethics Committee (HREC), and written approval obtained, before volunteers are recruited and patients are enrolled. It is the responsibility of the Investigator to report study progress to the HREC as required or at intervals not greater than one year.

The Principal Investigator, or his/her nominee, will be responsible for reporting any serious adverse events to the HREC as soon as possible, and in accordance with the local guidelines of the HREC.

11.3 Protocol Amendments

Protocol modifications that impact on patient safety or the validity of the study will be approved by the HREC. If a Protocol amendment requires changes to the Informed Consent Form, the revised Informed Consent Form, prepared by the Investigator, must be approved by the HREC.

The original signed copy of amendments will be kept in the Study File with the original Protocol. It should be noted that where an amendment to the Protocol substantially alters the study design or the potential risks to the patients, each Patient's consent to continue participation should be obtained.

11.4 Protocol Compliance

The instructions and procedures specified in this Protocol require diligent attention to their execution. If any patient is treated in a manner that deviates from the Protocol, the nature and reasons for the Protocol violation shall be recorded as a note to file and kept in the site study files. The Investigator and designees will comply with all applicable federal, state and local laws.

12 Photography / Fluorescein Angiography

12.1 Fundus Photography

Fundus camera photography for FFAs and colour photographs are to be performed digitally. All digital images will be de-identified for grading.

12.2 Fundus Colour Photographs

Non stereo 3-Field, ETDRS digital images should be captured at an angle of 30 degrees. If the 30 degrees angle is not an option then 35 degrees can be used. Images will be taken at baseline, week 5, week 16 and 6 month follow up visit or early exit visit.

12.3 Fluorescein Angiography

Fluorescein injection: 5ml of 10% sodium fluorescein will be rapidly injected into the antecubital vein. Other injection sites may be substituted if necessary.

Standard angiogram will be presented as 4 UP (RF, <30sec, 60-90 sec, 5 min) at baseline, Week 5 and week 16 or early exit visits.

13 Optical Coherence Tomography & Fundus Autofluorescence

13.1 OCT Examination Procedure

The eyes should be maximally dilated to help ensure optimal quality scans.

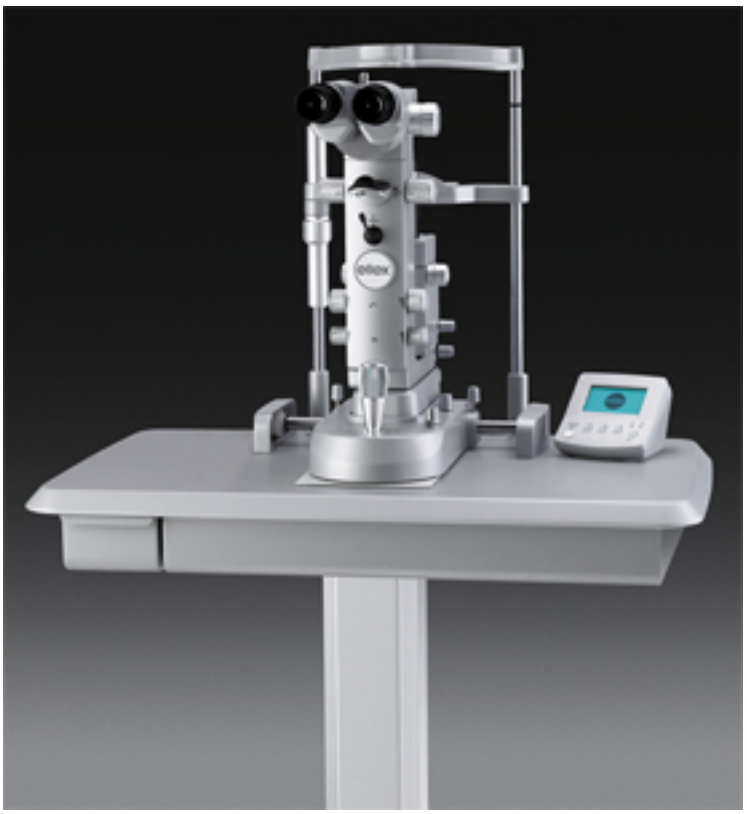
Spectralis OCT: The volume scan is used to calculate the different thickness map parameters for statistical analysis of the outcome data. Cross hair Scan of both horizontal and vertical line is used to demonstrate cystic macular oedema

Cirrus OCT: The Macula Thickness: Macula Cube 512 x 128 scan is used to calculate the different thickness map parameters for statistical analysis of the outcome data. The HD 5 Line Raster is used to demonstrate cystoid macula oedema.

13.1 Fundus Autofluorescence Procedure

Must be performed prior to fluorescein angiography. Non stereo, Fundus Autofluorescence images should be captured at an angle of 35 degrees with the Heidelberg Spectralis or Zeiss Topcon using the Autofluorescence setting. The images should be captured using the ART mode. Autofluorescence is performed at the baseline, Week 5 and week 16 or early exit visits.

14 Ellex Integre NIR Laser



15 Schedule of Visits

	Screen Baseline Tue[i] or Fri[i]	Wk1[a], 2, 3 & 4 Mon[a], & Wed	Wk1, 2,3 & 4 Fri	Wk 5 Mon Final Laser Rx	Wk 5 Tue Final Laser on Board Assessments	Wk 8	Wk 12	Wk 16	6 month Safety Follow Up post last laser	Early Exit
Visit Window						+/- 1wk	+/- 1 wk	+/-1 wk	+/- 2 wk	
Informed consent	X									
Treatment allocation	X									
Con Meds	X		X		X	X	X	X	X	X
Adverse Events & Concomitant Procedures		X	X		X	X	X	X	X	X
Blood pressure	X				X	X		X	X	X
LogMAR BCVA	X				X			X	X	X
LogMar VA	X		X[c]		X	X	X	X	X	X
Microperimetry	X[h]	X[g,c, h]			X	X		X	X	
IOP	X				X			X	X	X
Dilated fundal examination	X		X[c]		X	X	X	X	X	X
Cataract grading	X		X[c]		X	X	X	X	X	X
OCT	X		X[c]	X[b]	X	X	X	X	X	X
Fundus Colour Photography	X				X			X	X	X
Autofluorescence	X[f]				X[f]			X[f]	X[f]	X[f]
Fluorescein angiography	X[e]				X			X		X
Urine Pregnancy Test	X[d]									
NIR Laser Treatment		X	X	X[b]						

a No NIR visit or treatment on Monday of week 1. Wednesday of Week 1 (i.e. 1st NIR treatment visit) must occur the week following the screening visit.
b Must be done the day prior to the Final assessments visit laser on board visit
c Must be done prior to laser treatment
d Required for women of childbearing potential.
e A suitable angiogram performed within 1 month prior to the baseline visit may be used
f Must be performed prior to fluorescein angiography
g Wednesday of Week 1 only
h At the investigators discretion any participant that did not have microperimetry performed on the study at baseline and week 1, however had standard of care microperimetry at similar timepoints before receiving their first NIR treatment, may be approached for their consent to use this data for study analysis. Participant consent will be obtained by signing an addendum study consent form allowing for the use of this standard of care microperimetry data in the study analysis.
i If clinics/staff are not available for baseline assessment on Tuesday or Friday, another day in the week immediately prior to starting NIR treatment may be selected, however the remaining treatment and visit schedule must be adhered to according to the protocol.

16 Appendices:

16.1 References (General)

- Nucleus Network, Standard Operating Procedures (SOPs) to achieve Good Clinical Practice (GCP) in Australian Clinical Research, V1.0, 17 September 2007

Research Plan-Background

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