

MERLOT

a study of epimacular brachytherapy for AMD

Macular EpiRetinal Brachytherapy versus Lucentis[®] Only Treatment (MERLOT)

A randomised controlled trial of epimacular brachytherapy versus ranibizumab monotherapy for the treatment of subfoveal choroidal neovascularisation associated with wet age-related macular degeneration in patients who have commenced anti-VEGF therapy

STUDY SPONSOR:
King's College Hospital

EUDRACT NO:
2009-012509-20

REC No:
09/HO206/21

CLINICALTRIALS.GOV
NCT01006538

VERSION: 5.0
9TH MAY 2011

I have read and agree to follow the study procedures as outlined in this protocol.

Print Name of Investigator

Investigator's Signature

Date

Sponsor:

King's College Hospital NHS Foundation Trust
Jackie Pullen
The Joint Clinical Trials Office,
F 16 Tower Wing
Guy's Hospitals
London SE1 9RT

Tel: 020 7188 5732
Fax: 020 7188 8330
Email: Jackie.pullen@kcl.ac.uk

Chief Investigator

Tim Jackson, PhD, FRCOphth
Honorary Consultant Vitreoretinal Surgeon
HEFCE Senior Clinical Lecturer
King's Health Partners
London SE5 9RS

Tel: 020 3299 1297
Fax: 020 3299 1721
Email: t.jackson1@nhs.net

Trial Manager

Riti Desai
Ophthalmology Research office
1st Floor, Normanby Building
King's College Hospital
London SE5 9RS

Tel: 020 3299 1297
Fax: 020 32991721
Email: ritidesai@nhs.net

Data Monitoring Committee

Desmond Archer OBE FRCS FRCOphth FMedSci
Emeritus Professor of Ophthalmology
The Queen's University of Belfast
ICS Block A, RVH
Belfast BT12 6BA
(Chair) (Clinician)

Tel: 028 90633325
Fax: 028 90632699
Email: d.archer@qub.ac.uk

Catey Bunce DSc
Medical Statistician
Moorfields Eye Hospital
London EC1V 2PD
(Statistician)

Tel: 020 7566 2820
Fax: 020 7566 2019
Email: c.bunce@ucl.ac.uk

David Charteris MD, FRCOphth
Consultant Vitreoretinal Surgeon
Moorfields Eye Hospital
London EC1V 2PD
(Clinician)

Tel: 020 7566 2251
Fax: 020 7566 2019
Email: david.charteris@moorfields.nhs.uk

Trial Steering Committee

Helen Jackman
Chief Executive
Macular Disease Society
PO Box 1870, Andover
Hampshire SP10 9AD
(Users' Representative)

Tel: 01264 350551
Fax: 01264 350 558
Email: helen@maculardisease.org

Usha Chakravarthy MD, PhD
Professor of Ophthalmology and Vision
Science, Centre for Vision Science
The Queen's University of Belfast
ICS Block A, RVH
Belfast BT12 6BA
(Clinician)

Tel: 02890632527
Fax: 02890632699
Email: u.chakravarthy@qub.ac.uk

Alistair Laidlaw MD FRCS FRCOphth
Consultant Vitreoretinal Surgeon
Lead Clinician in Ophthalmology
St Thomas' Hospital
London SE1 7EH
(Clinician)

Tel: 020 7188 4320
Email: Alistair.Laidlaw@gstt.nhs.uk

Zdenek Gregor MD, FRCOphth

Consultant Vitreoretinal Surgeon and
Former Director Medical Retina Service
Moorfields Eye Hospital
London EC1V 2PD
(Clinician)

Tel: 020 7566 2022
Fax: 020 7566 2019
Email: zdenek.gregor@moorfields.nhs.uk

Dr Toby Prevost
Reader in Medical Statistics
Department of Primary Care & Public
Health Sciences
School of Medicine, King's College
Floor 7, Capital House, 42 Weston St
London SE1 3QD, UK
(Trial Statistician)

Telephone: 0207 848 6799
Email: toby.prevost@kcl.ac.uk

Tim Jackson, PhD, FRCOphth
Honorary Consultant Vitreoretinal Surgeon
HEFCE Senior Clinical Lecturer
King's Health Partners
London SE5 9RS
(Chief Investigator)

Tel: 020 3299 1297
Fax: 020 3299 1721
Email: t.jackson1@nhs.net

Cornelius Lewis PhD
Director of Medical Physics
King's College Hospital
London SE5 9RS
(Radiation Safety Officer)

Tel: 020 3299 1646
Fax: 020 3299 3314
E-mail: cornelius.lewis@kcl.ac.uk

Barney Reeves DPhil (Oxon), MFPHM
Professorial Fellow, Health Services
Research

Clinical Trials and Evaluation Unit
Bristol Royal Infirmary, Level 7
Bristol BS2 8HW
(Epidemiologist)

Tel: 0117 342 3143
Fax: 0117 929 9737
Email: Barney.Reeves@bristol.ac.uk

Richard Wormald MA MSc (Epid) FRCS
FRCOphth
Consultant Ophthalmologist
Moorfields Eye Hospital
162 City Road
London EC1V 2PD
(Chair) (Clinician)

Tel: 020 7566 2256
Fax: 020 7566 2972
Email: r.wormald@ucl.ac.uk

Trial Statisticians

Dr Toby Prevost
Reader in Medical Statistics
Department of Primary Care & Public
Health Sciences
School of Medicine, King's College
Floor 7, Capital House, 42 Weston St
London SE1 3QD, UK
(Trial Statistician)

Telephone: 0207 848 6799
Email: toby.prevost@kcl.ac.uk

Reading centres

Central Angiographic Resource Facility
(London-Liverpool-Belfast)
Ophthalmic Research Centre
Queen's University of Belfast
Belfast BT12 6BA

Tel: 028 9063 2516 and 028 9063 2621
Fax: 028 9063 2666
Email: carf@qub.ac.uk

ABBREVIATIONS

AMD	Age-Related Macular Degeneration
ANOVA	Analysis of Variance
AREDS	Age Related Eye Disease Study Protocol
BCVA	Best Corrected Visual Acuity
CARF	Central Angiographic Reading Facility
CLGP	Clinical Lens Grading Protocol
CNV	Choroidal Neovascularisation
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FA and FFA	Fluorescein Angiography
GCP	Good Clinical Practice
Gy	Gray
HUI [®]	Health Utilities Index Questionnaire
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IOP	Intraocular pressure
ITT	Intent-to-treat
LOCF	Last-observation-carried-forward
MHRA	Medicines and Healthcare products Regulatory Agency
OCT	Optical Coherence Tomography
PDT	Photodynamic Therapy
PED	Pigment Epithelial Detachment
PPA	Per-protocol analyses
PSC	Posterior Subcapsular Cataract
PtID	Subject Identification
RAP	Retinal Angiomatous Proliferation
RPE	Retinal Pigment Epithelium
Sr ₉₀	Strontium 90
SOP	Standard Operating Procedure
VEGF	Vascular Endothelial Growth Factor
VFQ-25	The National Eye Institute 25-Item Visual Function Questionnaire

TABLE OF CONTENTS

ABBREVIATIONS	6
1 INTRODUCTION AND RATIONALE	14
1.1 Age Related Macular Degeneration	14
1.2 Disease Progression	14
1.3 Underlying Causes of Choroidal Neovascularisation	16
1.4 Current Therapy for Subfoveal CNV Secondary to AMD	16
1.5 Sr90 Applicator for the Treatment of Subfoveal AMD	17
2 DEVICE DESCRIPTION	20
2.1 Overview	20
2.2 Radiation Dose Characterisation	21
3 PRECLINICAL TESTING	22
3.1 Initial Procedure Evaluation	22
3.2 Radiation Dose Toxicity Study.....	23
3.3 Preclinical Simulation	25
4 CLINICAL TESTING	27
4.1 Subretinal Clinical Experience	27
4.2 Epiretinal Clinical Experience	28
4.2.1 Protocol NVI-068-International Feasibility Study	29
4.2.2 Protocol NVI-111-International Feasibility Study	33
4.3 Study Rationale	37
4.4 Risk vs. Benefits.....	38
5 INVESTIGATIONAL PLAN	40
5.1 Trial Design	40
5.2 Study Objective	41
5.3 Safety Parameters	41
5.3.1 Radiation Retinopathy	41
5.4 Efficacy Parameters	41
5.5 Subject Population	42
5.5.1 Informed Consent	42
5.5.2 Subject Screening	42
5.5.2.1 Inclusion Criteria	42
5.5.2.2 Exclusion Criteria	45
6 STUDY PROCEDURES BY VISIT	46
6.1 Cataract assessment and surgery	47
6.2 Screening.....	48
6.3 Baseline	49
6.4 Monthly Subject Visits.....	50
6.5 Health Economic Questionnaires	51
6.6 Merlot Visit Schedule	52
7 STUDY CONDUCT	56
7.1 Investigator Responsibility	56
7.2 Radiation Licensing/Certification	56
7.3 Regulatory Authority and Ethics Committee Approval.....	57

7.4	Subject Identification Number.....	57
7.5	Screen Failures	58
7.6	Protocol Deviations	58
7.7	Re-Treatment Criteria.....	59
7.8	Withdrawal.....	60
8	DESCRIPTION OF INVESTIGATIONAL INTERVENTION ..	61
8.1	Lucentis® Therapy	61
8.2	VIDION® System.....	62
8.2.1	Preparation of the VIDION® System.....	63
8.2.2	Radiation Monitoring.....	63
8.2.3	Device Malfunction.....	63
8.2.4	Anaesthesia	63
8.2.5	Pretreatment Planning.....	64
8.2.6	Vitrectomy Procedure	64
8.2.7	Radiation Delivery	65
8.2.8	Treatment Time	66
8.2.9	Probe Removal.....	66
8.2.10	Injection of Lucentis® Therapy After Radiation delivery.....	66
8.2.11	Closure.....	66
8.2.12	Post-Op Regimen	67
9	EVALUATION OF EFFICACY	67
9.1	ETDRS Best-Corrected Visual Acuity (BCVA)	67
9.2	Fundus Fluorescein Angiography (FFA) and Colour Fundus Photography.....	68
9.3	Optical Coherence Tomography (OCT)	69
10	ADVERSE EVENT REPORTING AND DOCUMENTATION .	70
10.1	Adverse Events Reporting.....	70
	Reporting of SAEs, SARs and SUSARs as multi-centre study.....	71
	Contact details for submission of SAEs, SARs and SUSARs at JCTO:	71
	Reporting Responsibilities	71
10.2	Adverse Event Documentation	72
10.3	Adverse Event Criteria	73
10.3.1	Intensity.....	73
10.3.2	Relatedness	73
10.3.3	Outcome	74
10.3.4	Treatment or Action Taken	74
11	STATISTICAL ANALYSIS	75
11.1	Study Design and Randomisation.....	75
11.2	Sample size calculation	75
11.3	Study Endpoints	77
11.3.1	Co-primary Endpoint- Treatment Success.....	77
11.3.2	Secondary Endpoints	77
11.4	Safety	78
11.5	Interim Analyses	78
12	QUALITY ASSURANCE, DATA HANDLING AND RECORD RETENTION.....	78

13	DATA MONITORING COMMITTEE AND TRIAL STEERING COMMITTEE.....	79
13.1	Data monitoring committee (DMC).....	79
13.2	Trial Steering Committee.....	79
14	INFORMED CONSENT.....	79
15	DATA MANAGEMENT.....	81
16	DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS ..	82
17	RECORDKEEPING.....	82
18	PUBLICATION POLICY AND FINANCIAL ASPECTS.....	83
19	INVESTIGATOR REPORTS	84
19.1	Adverse Event Report	84
20	REFERENCES.....	84

and surgery

APPENDIX I: VIDION OPERATOR’S MANUAL

APPENDIX II: LOCS II LENS GRADING PROTOCOL

APPENDIX III: ASSESSMENT OF BEST CORRECTED ETDRS VISUAL ACUITY

APPENDIX IV: THE DATA MONITORING COMMITTEE (DMC) CHARTER

APPENDIX V: THE NATIONAL EYE INSTITUTE 25-ITEM VISUAL FUNCTION QUESTIONNAIRE (VFQ-25)

APPENDIX VI: HEALTH UTILITIES INDEX (HUI®) QUESTIONNAIRE

Title	<u>Macular EpiRetinal Brachytherapy versus Lucentis Only Treatment (MERLOT)</u>
Objective	The objective of the MERLOT Trial is to evaluate the safety and efficacy of focal delivery of radiation for the treatment of subfoveal choroidal neovascularisation (CNV) associated with established wet age-related macular degeneration (AMD) previously treated with anti-VEGF therapy.
Hypothesis	It is hypothesised that epimacular brachytherapy will reduce the frequency of ranibizumab (Lucentis®) re-treatment that patients require, whilst maintaining visual acuity.
Indication For Use	Epimacular brachytherapy is indicated for the treatment of subjects with subfoveal CNV associated with wet AMD
Study Design	The MERLOT Trial is a multi-centre, randomised, controlled clinical study of epimacular brachytherapy for the treatment of subfoveal choroidal neovascularisation associated with wet age-related macular degeneration in patients who have been previously treated with ranibizumab.
Efficacy Endpoints	<p>Co-Primary outcome measures</p> <ol style="list-style-type: none"> 1. Mean change in ETDRS best-corrected visual acuity 2. Mean number of re-treatment injections of Lucentis® per patient, per year. <p>Secondary outcome measures</p> <ol style="list-style-type: none"> 3. Percentage of subjects losing < 15 ETDRS letters 4. Percentage of subjects gaining ≥ 0 ETDRS letters 5. Percentage of subjects gaining ≥ 15 ETDRS letters 6. Change in total lesion size by fluorescein angiography 7. Change in total CNV size by fluorescein angiography 8. Foveal thickness measured using OCT.
Safety Assessment	Incidence and severity of adverse events (AE) and ocular AEs. Incidence of cataract changes. Incidence of radiation induced toxicity.
Study Population	
Number of Subjects	A total of 363 eyes in 363 subjects
Inclusion criteria	<ol style="list-style-type: none"> 1. Subjects with subfoveal choroidal neovascularisation associated with wet age-related macular degeneration. Retinal Angiomatous Proliferation (RAP) lesions not directly involving the fovea must be associated with contiguous foveal leakage demonstrated on fundus examination, OCT, or fluorescein angiography;

-
2. Subjects must have received anti-VEGF induction treatment, defined as the first three months of anti-VEGF therapy. Following this induction period, subjects must have received at least 4 additional injections of Lucentis[®] in no more than 12 months preceding enrolment, or 2 additional injections of Lucentis[®] in no more than 6 months preceding enrolment, given on an as needed basis (for subjects who have received both Avastin[®] and Lucentis[®] treatment please see Section 5.5.2.1);
 3. At the time subjects commenced anti-VEGF therapy for wet age-related macular degeneration they were aged 50 years or older and met the NICE treatment criteria for Lucentis[®] therapy, as outlined in the Final Appraisal Determination (FAD). This states that all of the following circumstances must apply in the eye to be treated:
 - the best-corrected visual acuity is between 6/12 and 6/96 (24 to 69 ETDRS letters)
 - there is no permanent structural damage to the central fovea
 - the lesion size is less than or equal to 12 disc areas in greatest linear dimension
 - there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes)

Exclusion criteria

1. Patients who have not been treated in accordance with NICE guidance;
2. Visual acuity worse than 6/96 (24 ETDRS letters) at the time of study enrolment;
3. Subjects with prior or concurrent subfoveal CNV therapy with agents, surgery or devices (other than Macugen[®], Avastin[®], or Lucentis[®]) including thermal laser photocoagulation (with or without photographic evidence), photodynamic therapy, intravitreal or subretinal steroids, and transpupillary thermotherapy (TTT);
4. Subfoveal scarring;
5. Subjects with active concomitant disease in the study eye, including uveitis, presence of pigment epithelial tears or rips, acute ocular or periocular infection;
6. Subjects who have been previously diagnosed with Type 1 or Type 2 Diabetes Mellitus. Subjects who do not have a documented diagnosis, but have retinal findings consistent with Type 1 or Type 2 Diabetes Mellitus;
7. Subjects with advanced glaucoma (greater than 0.8 cup:disk) or intraocular pressure \geq 30 mmHg in the study eye;
8. Previous glaucoma filtering surgery in the study eye;

-
9. Subjects with inadequate pupillary dilation or significant media opacities in the study eye, including cataract, which may interfere with visual acuity or the evaluation of the posterior segment;
 10. Current vitreous haemorrhage in the study eye;
 11. History of rhegmatogenous retinal detachment or macular hole in the study eye;
 12. Subjects who present with CNV due to causes other than AMD, including subjects with known or suspected idiopathic polypoidal choroidal vasculopathy (IPCV), ocular histoplasmosis syndrome, angioid streaks, multifocal choroiditis, choroidal rupture, or pathologic myopia (spherical equivalent ≥ 8 Dioptre or axial length ≥ 25 mm);
 13. Subjects who have undergone any intraocular surgery in the study eye within 12 weeks prior to the screening visit, with the exception of cataract surgery as discussed in the Exclusion Criteria #14
 14. Previous cataract surgery within 2 months prior to enrolment into the study;
 15. Subjects with known serious allergies to fluorescein dye used in angiography;
 16. Subjects with known sensitivity or allergy to Lucentis[®];
 17. Subjects who underwent previous radiation therapy to the eye, head or neck;
 18. Subjects with an intravitreal device or drug in the study eye;
 19. Subjects with any other condition, which in the judgment of the investigator would prevent the subject from completing the study (e.g. documented diagnosis of dementia or serious mental illness);
 20. Current participation in another drug or device clinical trial, or participation in such a clinical trial within the last year;
 21. History of use of drugs with known retinal toxicity, including: chloroquine (Aralen – an anti-malarial drug), hydroxychloroquine (Plaquenil), phenothiazines, chlorpromazine (Thorazine), thioridazine (Mellaril), fluphenazine (Prolixin), perphenazine (Trilafon), and trifluoperazine (Stelazine);
 22. Subjects who are unwilling or unable to return for scheduled treatment and follow-up examinations for three years;
 23. Women must be post-menopausal ≥ 1 year unless surgically sterilised.

Treatment

Subjects will be randomised in a 2:1 ratio to Arm A (treatment) or Arm B (control):

Arm A: A single surgical procedure with epimacular brachytherapy using the VIDION[®] System, with Lucentis[®] (0.5 mg) administered on a monthly basis as required, using the re-treatment criteria below.

Arm B: Lucentis[®] (0.5 mg) administered on a monthly basis as required, using the re-treatment criteria below.

Re-Treatment Criteria

Lucentis should be administered if any of the following four conditions are met:

- The subject has lost more than five ETDRS letters of visual acuity from baseline, and this is attributable to active wet AMD;
- An increase of more than 50 microns in central retinal thickness from the lowest central retinal thickness measurement secondary to new or increased subretinal, intraretinal, or sub-RPE fluid, as confirmed by OCT;
- Presence of new, or an increase from the last visit in subretinal or intraretinal blood;
- New neovascularisation as confirmed by fluorescein angiography

Lucentis® should be administered at Baseline for subjects in both Arm A (VIDION®) and Arm B (Lucentis® monotherapy) if the above re-treatment criteria apply. To determine if there is new disease activity or loss of visual acuity, Baseline and Screening observations should be compared to recent clinical observations. Baseline treatment with Lucentis® in Arm A can be given concomitantly at the end of surgery, as detailed in Section 8.2.10, or given up to 21 days from the Screening Visit. At subsequent visits the observations used for retreatment decisions should be compared to other observations made during the subject's participation in the trial. Further details and clarification are provided in Section 7.7.

If the treating ophthalmologist decides that Lucentis® re-treatment would be beneficial for persisting subretinal, intraretinal, or sub-RPE fluid confirmed on OCT, but the re-treatment criteria are not fulfilled, then he or she may administer Lucentis®, but this should be recorded as a deviation.

If the eye does not show a decrease in fluid after three consecutive monthly injections, the treating ophthalmologist may choose to suspend treatment. Treatment may be re-initiated if the subretinal, intraretinal, or sub-RPE fluid becomes worse (relative to the visit when treatment was suspended) on OCT.

Number of Centres

Approximately thirty five UK centres

1 INTRODUCTION AND RATIONALE

1.1 Age Related Macular Degeneration

Age-Related Macular Degeneration (AMD) is one of the leading causes of adult visual loss in the developed world. AMD occurs in a non-neovascular, atrophic “dry” form or neovascular “wet” form. Patients with “dry AMD” have subretinal deposits (drusen), pigment changes, and some retinal atrophy, but their central vision is either preserved or deteriorates slowly. Approximately 10% of patients with the “dry” form of AMD progress to the “wet” form, characterised by Choroidal Neovascularisation (CNV), or overgrowth of new blood vessels under the retina. These vessels leak fluid that causes scar tissue to form, which in turn compromises vision, typically the central vision that is essential for reading and functioning. Patients who manifest the neovascular form of AMD represent the majority who develop legal blindness [defined as Best Corrected Visual Acuity (BCVA) of worse than 6/60 in the better-seeing eye]. Loss of vision has a major impact on the quality of life and independence for those afflicted, causing both economic and personal hardship.

1.2 Disease Progression

Early AMD

In the early stages of macular degeneration, the transport of nutrients and wastes by the RPE slows down. As waste products accumulate under the retina, they form yellowish deposits called drusen. Patients that develop this early form of AMD have a 1.3% chance of progressing to advanced AMD in five years.¹

Non-neovascular degeneration (also known as “dry” AMD) is a slow progressive condition characterised by the accumulation of drusen in the retina with some visual loss. As portions of the RPE continue to slow down nutrient and waste transport, the overlying photoreceptors become damaged. The size and number of drusen in the macula increase. Vision may be affected as RPE and photoreceptor cells are lost due to atrophy.

Neovascular AMD (“Wet” AMD)

CNV is the process through which the vessels from the choriocapillaris perforate and grow through Bruch's membrane and enter the subretinal pigment epithelial and/or subretinal spaces. When these new CNV membranes leak or rupture, the accumulation of fluid and blood together with the subsequent scarring seriously impairs or destroys the photoreceptor layer.^{2, 3}

Classification of the different types of neovascular AMD arose out of the Macular Photocoagulation Study (MPS), a series of clinical trials that evaluated laser treatment for selected patients with neovascular AMD. Neovascular AMD was identified as either classic or occult or as a combination of the two forms based on fluorescein angiography.

Classic CNV

Classic CNV was defined as lesions having angiographic findings in which the CNV is recognised as an area of bright, well-demarcated hyperfluorescence. The location of well-demarcated CNVs was further broken into three categories, as follows:

- Extrafoveal - CNV is 200 microns or more from the foveal centre
- Juxtafoveal - CNV is between 1 and 199 microns from the foveal centre
- Subfoveal - CNV is under the foveal centre.

Occult CNV

Occult CNV was defined as lesions having angiographic findings characterised by a fibrovascular retinal pigment epithelial detachment and/or late leakage of an undetermined source.

Mixed CNV

Mixed CNV was defined as a mixture of classic and occult neovascular patterns on the fluorescein angiogram. The CNV is considered *predominantly classic CNV* if the area of classic CNV represents more than 50% of the lesion or *minimally classic* if less than 50% of the lesion.

1.3 Underlying Causes of Choroidal Neovascularisation

Several hypotheses of pathogenesis have been proposed for the progression of AMD and the formation of choroidal neovascular membranes (CNVM). Hypotheses include primary RPE and Bruch's membrane senescence, primary genetic defects, and primary ocular perfusion abnormalities. Oxidative insults have also been proposed as a contributing factor.⁴⁻⁷

Although the underlying mechanism is not universally agreed upon, whatever the initial stimulus for CNVM formation, it is clear that angiogenic growth factors are ultimately involved.⁸⁻¹⁰ Postmortem surgically excised CNVM tissue and RPE cells have been shown to be immunoreactive for various growth factors that are thought to be angiogenic (e.g., vascular endothelial growth factor [VEGF], transforming growth factor-beta [TGF- β], platelet-derived growth factor [PDGF], basic fibroblast growth factor [bFGF]). Vascular endothelial cell proliferation, migration, and capillary formation are known to be stimulated by these angiogenic growth factors.

1.4 Current Therapy for Subfoveal CNV Secondary to AMD

The current standard of care for neovascular AMD is antiangiogenic therapy. Two compounds have been approved for use to treat AMD, one of which is an aptamer (Macugen[®]) specifically designed to bind VEGF₁₆₅, while the other is a humanised antigen binding fragment (Fab) (Lucentis[®]) that binds various isoforms of VEGF-A. A third antiangiogenic compound, Avastin[®], which is a full-length anti-VEGF antibody is being used widely off-label.

Macugen[®] was the first antiangiogenic agent with proven efficacy in clinical trials for neovascular AMD. It is an RNA aptamer that selectively binds VEGF₁₆₅. The efficacy of pegaptanib in 3 line vision loss from subfoveal CNV due to AMD was demonstrated by the VISION trials, which showed a treatment benefit across all lesion subtypes and sizes (up to 12 disc areas).¹¹ The proportion of patients who avoided 3-line vision loss at 1 year was 70% in the pegaptanib-treated group vs 55% in the control group.

Lucentis[®] has been studied in three randomised, controlled, Phase III clinical trials (MARINA, ANCHOR, PIER).^{12, 13, 14} The MARINA and ANCHOR trials studied monthly injections of 0.5 and 0.3 mg of Lucentis[®], while the PIER trial studied monthly injections for the first three months followed by quarterly injections thereafter. The ANCHOR and MARINA trials showed that the proportion of patients who avoided 3-line vision loss at 1 year was approximately 95%, while the PIER trial data for the same set of patients was 90% avoiding 3-line loss. Both the monthly and the quarterly injection schedule is reflected in the prescribing information.¹⁵

Avastin[®] has not been licensed for the treatment of AMD and is currently being used off-label, although randomised clinical trials are underway in the US (CATT trial) and UK (IVAN trial).

1.5 Sr90 Applicator for the Treatment of Subfoveal AMD

Localised radiation treatment has the ability to prevent proliferation of vascular tissue^{16, 17} by inhibiting neovascularisation. After low-dose radiation, vascular endothelium demonstrates morphologic and DNA changes,¹⁸⁻²⁰ inhibition of replication,^{21, 22} increased cell permeability,^{23, 24} and apoptosis.²⁵ Fibroblast proliferation and subsequent scar formation, a hallmark of end-stage neovascular AMD, are also inhibited.¹⁷

CNV membranes, which contain endothelial cells that are proliferating due to the hypoxic environment and the chemokines that are produced are more sensitive to radiation treatment than the retinal vasculature and non-proliferating capillary endothelial cells and larger vessels.²⁶ Clinical experience with conventional fractionated irradiation for head and neck malignancies has shown that cumulative doses (multiple fractions) of up to 30 Gy cause no damage to the retina or optic nerve.²⁷ Indeed, early studies examining the effect of radiation in the eye have demonstrated that low dose radiation, while damaging CNV membranes, does not affect the overlying retina.^{28, 29} Furthermore, early publications report resolution of subretinal fluid, haemorrhages, and exudates after radiation therapy; and that vision was maintained in most subjects.²⁸⁻³⁰

The Ophthalmic Sr₉₀ Applicator used for the treatment of CNV associated with AMD offers potential advantages over standard radiation treatment and laser photocoagulation. In contrast to external beam radiotherapy, a larger dose can be delivered to the macula with less irradiation of normal ocular structures and surrounding tissues. And unlike laser photocoagulation, in which laser energy is used to coagulate the CNV membranes, there is no thermal injury to the retina or injury to the surrounding tissues since the Sr₉₀ Applicator is selective to proliferating cells and tissues.

Results of feasibility studies using ocular plaque applicators suggest the utility of ocular Sr₉₀ Applicators in the treatment of subfoveal CNV associated with AMD. In a prospective controlled study of 86 subjects, Jaakkola et al³¹ reported on the use of external strontium 90 plaque with single doses of 15 Gy and 12.6 Gy. Recent recalibration measurements have revealed that the actual dose delivered by Plaque I was 32.4 Gy instead of 15 Gy [NVI-0093]. The recalibration was performed by two groups, STEP/AEA-QSA and STUK (Finnish Centre for Radiation and Safety)]. The same calibration experiments confirmed the published dose of Plaque II as 12.6 Gy. The 32.4 Gy group demonstrated significantly more favourable visual acuity results as compared to the control group. The control group lost an average of 3.02, 3.95, and 4.90 lines at 6, 12, and 24 months, respectively, while the treated group lost 0.24, 0.82, and 2.41 lines. The 12.6 Gy group did not show a significant difference compared to the control, suggesting the higher dose is more effective. Neither treatment group differed significantly from controls at 36 months. Angiographically, in both treatment groups combined, the CNV was considered less active than at baseline in 76.9% of the treated subjects at 6 months, 77.1% at 12 months, and 75.0% at 24 months, compared to 43.2%, 71.4%, and 78.4% at 6, 12, and 24 months respectively. The macula was considered clinically dry in 37.5% of the treated subjects at 6 months, 56.4% at 12 months, and 43.6% at 24 months, compared to 2.3%, 21.1%, and 31.3% at 6, 12, and 24 months respectively.

In another study by Jaakkola et al,³² strontium 90 Plaque I was evaluated in a prospective, non-randomised clinical trial. A single dose of 29 Gy at a depth of 1.75 mm was used

(see explanation of calibration experiments above). The applicator was surgically introduced in the episcleral surface, under the macula and held in place manually for the treatment period of 54 minutes. Twenty subjects with recently diagnosed CNV received plaque applicator treatment and 12 subjects were followed as controls. At 12 months follow-up, 3 (15%) of the 20 Sr₉₀ Applicator-treated eyes experienced a decrease of six or more lines of visual acuity, as compared to 6 (50%) of the 12 non-treated eyes (p=0.057). The mean number of lines lost was 2.6 (SD 3.7) for treated eyes and 5.3 (SD 3.2) in non-treated eyes (p=0.024). No radiation-related adverse effects were noted.

In a second study, Finger et al,³³ treated 23 eyes of 23 subjects with ophthalmic plaque (palladium 103 using 1250 to 2362 cGy) therapy. Subjects were followed for a mean of 19 months (S.D. 10.7 months, range 3 to 37 months). Six months after treatment, three (16%) of 19 eyes had lost three or more lines of best-corrected visual acuity; in the 13 eyes examined 12 months after treatment, four eyes (31%) lost three or more lines of acuity, and 24 months after radiation therapy, only two (22% of nine eyes) lost three or more lines of visual acuity. No eye suffered sudden irreversible loss of central vision. No radiation retinopathy, optic neuropathy, or cataract could be attributed to radiotherapy within this follow-up period.

The absence of reports of radiation retinopathy, optic neuropathy, or cataract formation attributable to Sr₉₀ Applicator in these published studies of ocular plaque Sr₉₀ Applicator used in the management of subretinal CNV is consistent with the safety profile of Sr₉₀ Applicator for use in the treatment of ocular tumours.

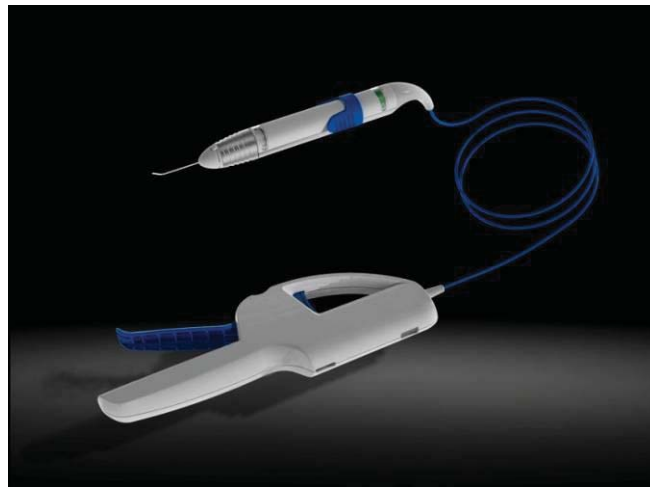
These findings support the clinical evaluation of Sr₉₀ in the management of CNV proposed in this clinical study protocol.

2 DEVICE DESCRIPTION

2.1 Overview

The VIDION[®] System is an intraocular Sr₉₀ applicator device intended to treat neovascularisation of retinal tissue by means of local, directional delivery of radiation to target tissues (see Figure 1).

FIGURE 1



VIDION[®] System (Image courtesy NeoVista Inc.)

Using standard vitreoretinal surgical techniques, the sealed radiation source is placed temporarily over the fovea in the vitreous cavity by means of a proprietary intraocular probe.

When in the storage (retracted) position, the radiation source is surrounded by materials designed to effectively protect the surgeon, staff, and subject during the handling and initial positioning. During treatment (source engaged), the source is located within a specially designed stainless steel tip that allows the radiation to reach the target tissues while the source is contained in a closed system. This local, focused delivery may allow for the treatment benefits of radiation with less toxicity to surrounding tissues.

The VIDION[®] operator's manual is provided in Appendix 1.

2.2 Radiation Dose Characterisation

The device design optimises the radiation dose curves to deliver therapeutic dosage to the CNV while protecting other critical ocular structures. Based on a target dose of 24 Gy at the peak of the distribution, Table 1 estimates the dose received by the lens, optic disc, optic nerve, and retina during treatment.

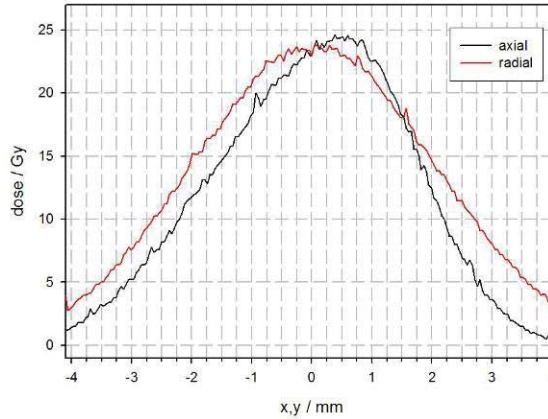
TABLE 1
Radiation Dose Received By Critical Structures

Structure	Maximum Dose	Estimated distance from target (i.e., fovea)*	Shortest distance to probe surface at source centre (considering probe dimensions)
Lens	0.56 mGy	>15 mm from choroid to posterior aspect of the lens	11.7 mm
Optic disc (closest edge)	6.3 Gy	3 mm optic disc edge to foveal centre	3.6 mm
Optic nerve	2.4 Gy	3.1 mm	3.6 mm
Retina – fovea	24 Gy	within a 1.5 mm diameter	
Retina – macula	23 Gy	within an annulus 1.5 to 6.0 mm diameter	
Retina - peripheral	8 Gy	Outside a 6.0 mm diameter circle	

*Distance estimates based on Jakobiec FA and Ozanics V, General topographic anatomy of the eye, in Duane's Foundations of Clinical Ophthalmology, Tasman W and Jaeger EA, Eds. 1999

The radiation dosimetry of the treatment area is characterised in Figure 2 below.

FIGURE 2



Dose Rate Profile of Delivery Device

3 PRECLINICAL TESTING

Device performance and functionality was assessed using both laboratory testing as well as animal models. Initial safety and feasibility assessments were undertaken in animal models, as described below.

3.1 Initial Procedure Evaluation

The feasibility of the subretinal intervention technique was evaluated in rabbits. Ten rabbits (ten eyes) were randomly selected to undergo the proposed treatment procedure using a dummy device (i.e., with no radiation source).

The experimental intervention was performed by a retinal surgeon using a standard pars plana vitrectomy under direct visualisation using a standard ocular surgical microscope and a vitrectomy lens. Infusion was accomplished through a pars plana scleral incision. A small bleb was created in the inferior retina with intentional creation of a controlled retinal detachment in this area. The radiation probe was inserted inside the vitreous cavity and into the bleb through a small retinotomy. The probe was placed subretinally over the intended target area, and steadily held in position for the duration of the

simulated intervention (two or five minutes). The probe was then withdrawn from the bleb and from the eye, the infusion removed, the sclerotomies closed and the conjunctiva sutured.

No major complications were observed during the procedures. By the third postoperative day all retinas (10/10;100%) had completely reattached. Each eye was evaluated both pre- and one-month postoperatively by electroretinography (ERG), fundus photography and fluorescein angiography, which showed no change except for minor pigmentary changes in the retinotomy area. There were no pigment, vascular, retinal or other changes in the target area, and no subretinal fluid accumulation. The retinotomy was closed and sealed in all ten eyes.

All rabbits were sacrificed one month after surgery. Enucleation and histology were performed on all eyes, which showed no significant changes in the retina, RPE, choriocapillaris, Bruch's membrane, or choroid when viewed by light microscopy.

The initial procedure evaluation study demonstrated that the surgical intervention as proposed was feasible and safe, with no complications observed in the intraoperative and postoperative period (follow-up of one month).

3.2 Radiation Dose Toxicity Study

The objective of this study was to evaluate and quantify the acute effects of beta radiation on retinal and subretinal tissue over a prescribed dose range by studying 120 rabbits (120 eyes) using the epiretinal approach.

Eighty (80) rabbits (80 eyes) were treated in eight groups of ten animals each. The study was designed to test the acute effects of targeted radiation at doses of 0 Gy (sham), 13 Gy, 19 Gy, 26 Gy, 32 Gy, 38 Gy, 51 Gy, and 77 Gy, but allowed simultaneous delivery of higher doses in additional study areas, allowing evaluation of dose effects through 246 Gy. An additional forty (40) rabbits (40 eyes) were evaluated with a follow-up of 12 and 24 weeks using the following dosages: 0 Gy (sham control), 26 Gy, 51 Gy, 77 Gy, 82 Gy,

164 Gy, and 246 Gy. Preoperative testing included fluorescein angiography, fundus photography, optical coherence tomography, ERG, and histology.

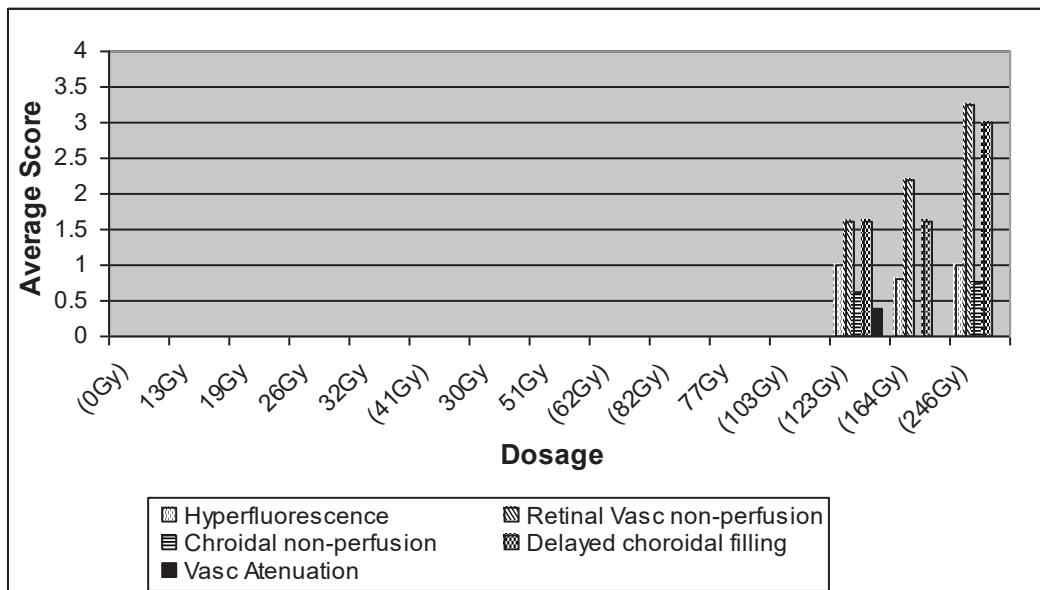
The procedure was performed under direct visualisation through a surgical microscope. The retinal surgeon inserted the probe into the vitreous cavity, and positioned it epiretinally over the target area with the tip facing the inferior retina one disc diameter away from the optic nerve. A polyamide depth gauge was connected to the tip of the probe to assure consistent distance from the source to the target area (1.5mm), and allowing for an additional study area of a higher dose immediately underneath the tip of the probe (the nearest point from the tip). The position was maintained throughout the procedures by closely monitoring the depth gauge contact through the microscope. Treatment times for each subgroup were calculated based on the known activity of the radiation source.

Forty (40) animals, five in each treatment group, underwent follow-up testing followed by sacrifice and histological evaluation at four weeks post treatment, and the remaining 40 animals at eight weeks post treatment. No clinical changes were seen in the target area for all doses through 103 Gy by fluorescein angiography, colour photograph at both follow-up time points, with no change between the time periods of four and eight weeks. Also, no functional changes were seen by electroretinography at either follow-up time point, with no change between the time periods of four and eight weeks. Histological evaluation was performed in dose areas up to 77 Gy, and demonstrated no significant changes in the retina, RPE, choriocapillaris, Bruch's membrane complex, or choroid when viewed by light and electron microscopy at both follow-up time points, with no significant change between the time periods of four and eight weeks. During the fluorescein angiography and fundus photography evaluations of the higher dose areas, changes were only apparent at 123 Gy and above. Fundus photography disclosed retinal vascular obliteration, myelin atrophy, vascular attenuation and hypopigmentation in the areas treated with 123 Gy, 164 Gy and 246 Gy, with changes becoming more pronounced in the higher dosage areas. Similarly, fluorescein angiography disclosed areas of hypofluorescence, retinal vascular non-perfusion, choroidal non-perfusion, delayed

choroidal filling and vascular attenuation, also becoming more pronounced in the higher dosage areas. There were no changes noted between the follow-up time periods of four and eight weeks.

Figure 3 below graphically demonstrates the changes observed on fluorescein angiography at the evaluated dosages. Changes were first noted at 123 Gy, indicating the threshold at which acute radiation damage can be expected to occur with intraocular radiation as delivered by the NeoVista® Ophthalmic System.

FIGURE 3
Toxicity Effects Noted on Fluorescein Angiography at Eight Weeks



In summary, no clinically significant acute changes were observed in the retinal or subretinal tissues at dosages up to 51 Gy at up to six months follow-up. There were progressive clinical changes in the subgroups receiving a single high dose of 82, 164 and 246 Gy between the follow up time periods of four and 24 weeks.

3.3 Preclinical Simulation

The effects of the proposed radiation dosage (i.e., 26 Gy) were evaluated following subretinal delivery in the canine model using the NeoVista® Ophthalmic System clinical procedure. A second objective was to evaluate the overall procedure prior to clinical use in an eye model with similar dimensions to the human eye. Canines (N=5) were selected for this study because of the similarities in ocular structure and size. Pretreatment testing included electroretinography (ERG), fluorescein angiography, fundus photography and optical coherence tomography (OCT).

The procedure was performed by a retinal surgeon using a standard pars plana vitrectomy under direct visualisation using a standard ocular surgical microscope and a vitrectomy lens. Placement was determined using the retinal touch-off method and positioning clips to mark the location at the depth of the retina. The retina was detached and a 5-6 mm bleb created in the area centralis as determined by fundus examination and vascular references during the procedure. Position spacers were used to assure probe replacement at 1.5 mm above the target area. Radiation was delivered subretinally to the simulated target area at the area centralis. Treatment time was calculated based on the known activity of the radiation source.

During the intraoperative period, immediately after the air fluid exchange, the retina was completely reattached in five out of five dogs. The retinotomy site was completely sealed and the retina was completely attached in four out of five dogs at the one week follow-up. At the one month follow-up, the retina was completely attached in all four dogs. No other complications were observed in any of the four dogs. In the dog with retinal detachment (first surgery) an inadvertent peripheral retinal tear was created during the surgery, resulting in a persistent partial retinal detachment unrelated to the radiation delivery and the institutional approval of this animal study did not allow a second surgical procedure.

Retinal function was evaluated by ERG, which remained normal in all four eyes with attached retina at one month follow-up. No significant changes in the retina, RPE/choriocapillaris/Bruch's membrane complex, or choroid of the treatment area were

seen by light and electron microscopy evaluation after the one month follow-up when compared to the fellow (non-treated) eye in all four dogs that presented attached retina at the one month follow-up. The one eye that presented retinal detachment at one month did not undergo histological evaluation.

Using the baseline fundus photography and fluorescein angiography of the treated eye for comparison, no changes were seen on the retina, retinal pigment epithelium, choriocapillaris, and choroid of the treatment area of all four dogs that presented attached retina at one month follow-up. There were no signs of ischaemia, non perfusion, vascular proliferation, vascular attenuation, leakage, pigmentary changes, neovascularisation, fluid accumulation fibrosis, exudates or haemorrhage in the treatment area of all four dogs.

Using the baseline optical coherence tomography (OCT) of the treated eye for comparison, no changes were seen in the retinal thickness of the treatment area of all four dogs that presented attached retina at the one month follow-up. The one eye that presented retinal detachment at one month did not undergo fundus photography, fluorescein angiography or OCT.

Thus retinal healing was not inhibited by radiation using the dosages proposed for clinical evaluation. At this dosage, no clinically significant acute changes were seen in the retina, RPE, choriocapillaris, or larger choroidal vessels based on ERG, fluorescein angiography, fundus photography, OCT or histological exam at one month. There was no damage to the optic disc or optic nerve.

It was also concluded that the surgical procedure proposed using the Sr₉₀ Applicator device is feasible and safe and allows for subretinal delivery of radiation for the treatment period proposed.

4 CLINICAL TESTING

4.1 Subretinal Clinical Experience

An initial feasibility study was conducted at Doheny Eye Institute, to evaluate a subretinal approach for delivery of radiation for the treatment of CNV in ten subjects.

While reduction in CNV leakage was observed in the majority of cases, surgical complications associated with the subretinal procedure precluded the expected improvements in visual acuities.

Over the course of the study, the incidence of adverse events decreased, and this was accompanied by improvement in visual acuity. It was determined that radiation delivered using the epiretinal approach may represent a less challenging surgical approach to radiotherapy of CNV. This hypothesis led to development of the current epiretinal system that is the subject of this clinical protocol.

4.2 Epiretinal Clinical Experience

A total of 61 subjects have been enrolled in two Phase II, non-randomised, multicentre studies of Sr₉₀ beta radiation (NVI-0068 and NVI-111), and a large, international, Phase III randomised clinical trial (CABERNET) is midway through recruiting 495 patients. These studies demonstrate a favourable safety profile with completed data sets also showing good visual results.

Study NVI-0068 is a non-randomised, multicentre trial evaluating the safety and effectiveness of delivering 15 Gy and 24 Gy by using the NeoVista® Ophthalmic System for the treatment of choroidal neovascularisation (CNV) in subjects with age-related macular degeneration.

Study NVI-111 is a non-randomised, multicentre trial evaluating the safety and effectiveness of delivering 24 Gy by using the NeoVista® Ophthalmic System with concomitant Avastin® for the treatment of choroidal neovascularisation (CNV) in subjects with age-related macular degeneration.³⁴

Subjects enrolled in these trials represented all AMD lesion subtypes, i.e., predominantly classic, minimally classic, and occult with no classic. Lesion size at time of enrolment was as large as 12 MPS disc areas and baseline visual acuity was required to be 6/18 to 6/120.

4.2.1 Protocol NVI-068-International Feasibility Study

A total of 34 subjects have been enrolled in NVI-0068, which is a non-randomised, multicentre trial evaluating the safety and effectiveness of delivering 15Gy and 24Gy by using the Epi-Rad₉₀TM Ophthalmic System for the treatment of choroidal neovascularisation (CNV) in subjects with age-related macular degeneration. Enrolment has been completed, and patient follow-up as well as data collection are ongoing. In the 8 subjects who received the 15Gy radiation dose, the lesion type was predominantly classic (n=3), minimally classic (n=3) or occult (n=2). In the 26 subjects who received the 24 Gy radiation dose, the lesion type was predominantly classic (n=11), minimally classic (n=6) or occult (n=9). Baseline visual acuity was 38 letters (range 15 to 67 letters)

Table 2 summarises the available Best Corrected Visual Acuity (BCVA) data for the Per Protocol Analysis patients who underwent 15 Gy epiretinal radiation, BCVA was stable for all eyes through to Month 12 and for 80% at Month 18 and Month 24. A gain of 15 or more letters was observed for one single eye at Month 1, Month 2, Month 3, Month 6 and Month 18.

Table 2
BCVA - PPA-LOCF
15 GY EPIRETINAL STUDY (N=5)

Measure	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24
Number of subjects	5	5	5	5	5	5	5	5
Vision Maintenance (% Losing <15 letters)	100%	100%	100%	100%	100%	100%	80%	80%
% Gaining 0 or more letters	3 (60%)	4 (80%)	3 (60%)	3 (60%)	2 (40%)	2 (40%)	3 (60%)	2 (20%)
% Gaining 15 or more letters	1 (20%)	1 (20%)	1 (20%)	1 (20%)	0%	0%	1 (20%)	0%
% Gaining 30 or more letters	0%	0%	0%	0%	0%	0%	0%	0%
% Losing 30 or more letters	0%	0%	0%	0%	0%	0%	1 (20%)	1 (20%)
Mean Change in VA (letters)	+3.8	+5.2	+5.0	+4.2	-2.4	-2.4	-4.4	-7.6

Per Protocol Analysis (PPA) population consists of all enrolled subjects who received treatment with the Epi-Rad90TM Ophthalmic System, had at least one post-treatment follow-up, and no major protocol violations.
LOCF- Last Observation carried forward

Table 3 summarises the BCVA data for per protocol patients who underwent 24 Gy epiretinal radiation. BCVA was stable for all eyes through to Month 3 and at Month 12. A single eye lost ≥ 15 letters at Months 9 and 18, and two eyes lost ≥ 15 letters at Months 6 and 24. A gain of at least 15 letters was observed for at least 3 eyes at each time point.

Table 3
ETDRS BCVA – PPA-LOCF
24 Gy EPIRETINAL STUDY (N=19)

Measure	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24
Number of subjects	19	19	19	19	18	18	18	18
Vision Maintenance (% Losing <15 letters)	19 (100%)	19 (100%)	19 (100%)	17 (89%)	17 (94%)	18 (100%)	17 (94%)	16 (89%)
% Gaining 0 or more letters	14 (74%)	15 (79%)	14 (74%)	13 (68%)	11 (61%)	13 (72%)	10 (56%)	8 (44%)
% Gaining 15 or more letters	7 (37%)	8 (42%)	10 (53%)	7 (37%)	5 (28%)	5 (28%)	4 (22%)	3 (17%)
% Gaining 30 or more letters	2 (11%)	2 (11%)	2 (11%)	2 (11%)	1 (6%)	1 (6%)	2 (11%)	1 (6%)
% Losing 30 or more letters	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mean Change in VA (letters)	+11.4	+11.4	+12.6	+7.5	+5.6	+9.4	+5.3	+2.3

Per Protocol Analysis (PPA) population consists of all enrolled subjects who received treatment with the Epi-Rad90™ Ophthalmic System, had at least one post-treatment follow-up, and no major protocol violations.

LOCF- Last Observation carried forward

** One subject was censored from Month 9 onwards as he was retreated with a 24 Gy dose

Table 4 summarises the adverse events (AEs) reported to date. Two (2) cases of subretinal fibrosis, one (1) case of RPE atrophy and one (1) retinal tear were attributed to the device by the study investigator. The two (2) cases of subretinal haemorrhage reported were transient, resolved without medical or surgical intervention, and there were no sequelae. The retinal tear was peripheral to the macula and was treated with thermal laser with no complication.

The adverse events reported in this study included seven (7) cases of reoccurrence of choroidal neovascularisation, 3 corneal abrasions, 1 case of epiretinal membrane, 1 case of intraretinal bleeding, 1 case of pigment on the lens, 2 cases of RPE atrophy, 1 case of

subconjunctival haemorrhage, 2 cases of subretinal fibrosis, 4 cases of moderate visual loss, 2 cases of vitreous haemorrhage, 1 case of large cotton wool spots, 1 case of retinal scarring, 1 case of retinal scarring, 1 case of submacular haemorrhage and 1 case of subretinal haemorrhage. The most frequently reported adverse event was cataract formation, which was observed in 14 subjects. These events were not unexpected since vitrectomy and radiation have been shown to cause new cataracts, or accelerate cataractogenesis. Of the 14 patients affected with cataract formation, 13 have elected phacoemulsification with intraocular lens placement to date. The surgeries were uneventful, with good clinical outcomes.

There were 4 cases of moderate vision loss, of which 2 were due to the progression of the cataracts. These cases resolved without sequelae subsequent to the phacoemulsification and IOL implantations. One subject had a posterior capsular opacification (which lead to the vision loss) and one other subject had moderate vision loss which was attributed to the progression of the AMD disease.

Table 4
All Ocular Adverse Events observed in the study
BOTH STUDY GROUPS- 15 GY AND 24 GY DOSES OF RADIATION (N=34)

Adverse Event	Number of Events Reported	Worst Severity	Relationship To the device	Was this event unanticipated?
Cataract	14	Severe	Not related	No
Corneal Abrasion	3	Moderate	Not related	No
Epiretinal Membrane	1	Mild	Not related	No
Intra retinal Blood	1	Mild	Possibly related	No
Moderate Vision loss (> 3 lines on ETDRS chart or 15 letters)	4	Moderate	Not related	No
Large Cotton Wool Spots	1	Mild	Not related	No
Pigment on lens	1	Mild	Not related	No
Reoccurrence of CNV	7	Severe	Not related	No
Retinal tear	1	Moderate	Probably Related	No
RPE Atrophy	2	Moderate	Possibly related in 1 case. Not related in the other	No
Retinal scarring	1	Moderate	Not Related	No
Subconjunctival haemorrhage	1	Moderate	Not related	No
Submacular haemorrhage	1	Mild	Not related	No
Subretinal fibrosis	2	Moderate	Possibly related	No
Subretinal haemorrhage	2	Moderate	Not related	No
Vitreous haemorrhage	2	Severe	Not related	No

4.2.2 Protocol NVI-111-International Feasibility Study

A total of 34 subjects have been enrolled in NVI-111, which is a non-randomised, multicentre trial evaluating the safety and effectiveness of delivering 24Gy by using the Epi-Rad₉₀TM Ophthalmic System with concomitant bevacizumab (Avastin[®]) for the treatment of choroidal neovascularisation (CNV) in subjects with age-related macular degeneration. Enrolment has been completed, and patient follow-up as well as data collection are ongoing. In the 34 subjects, the lesion type was predominantly classic (n=10), minimally classic (n=7) or occult (n=17). Baseline visual acuity was 41 letters (range 19 to 67 letters).

Table 5 summarises the BCVA data for the per protocol patients who underwent 24 Gy epiretinal radiation and received bevacizumab. BCVA was stable for at least 20 eyes (≥ 83%) through to Month 12. One single eye lost 15 letters or more at Month 9 and 12, and three (3) eyes lost 15 letters or more at Month 6. A gain of 15 or more letters was observed for a minimum of 8 eyes and a maximum of 14 eyes (range 33% to 58%) at each time point.

TABLE 5
ETDRS BCVA-ITT-AVAILABLE
24GY EPIRETINAL + BEVACIZUMAB STUDY (N=34)

Measure	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	Month 18
Number of subjects	34	34	33	34	34	31	34
Vision Maintenance (% Losing less than 15 letters)	100%	100%	97%	100%	85%	90%	91%
% Gaining 0 or more letters	76%	85%	85%	85%	76%	77%	68%
% Gaining 15 or more letters	15%	32%	61%	53%	47%	39%	38%
% Gaining 30 or more letters	6%	6%	15%	12%	9%	13%	12%
% Losing 30 or more letters	0%	0%	0%	0%	3%	0%	0%
Mean Change in VA (letters)	6.5	11.3	14.9	15.3	9.3	10.0	8.9
Standard Deviation (letters)	8.9	10.5	14.4	13.6	16.6	15.9	17.3

Intent to Treat (ITT) population consists of all enrolled subjects.. Available- All patient information that was available at the time of the analysis.

Visual acuity data from the NVI-111 data are shown graphically in Figure 4. There was a corresponding reduction in central retinal thickness demonstrated over twelve months of follow up (Figure 5). Subjects in the NVI-111 trial received an average of only 0.26 ‘as required’ Avastin® injections, based on disease activity, following the two peroperative Avastin® injections given as per protocol.

FIGURE 4

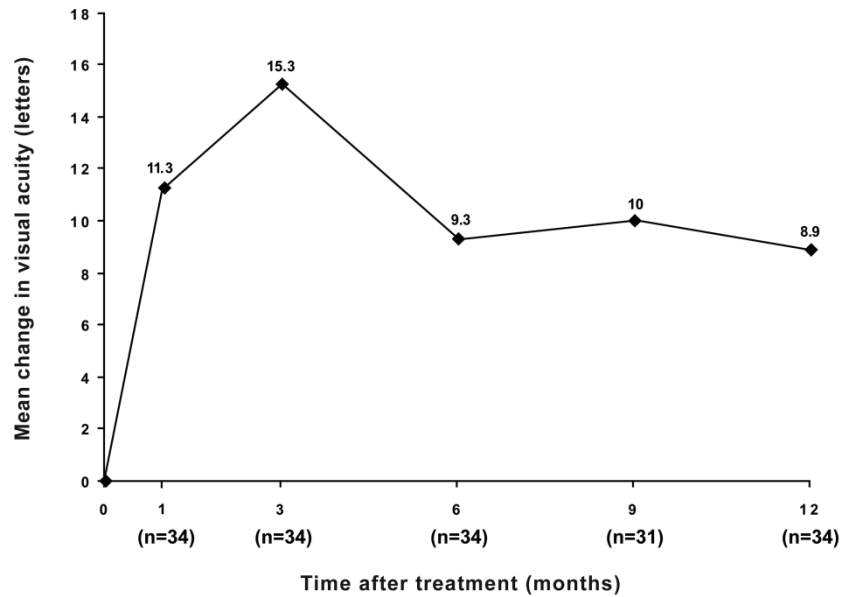


FIGURE 5

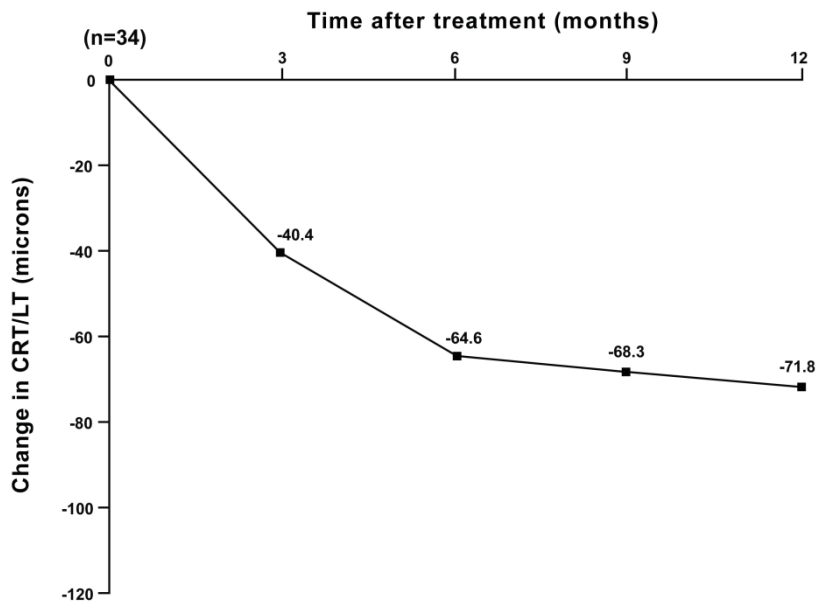


Table 6 summarises the adverse events (AEs) reported to date. One case of subretinal haemorrhage was attributed to the device which occurred outside of the lesion area while the surgeon was withdrawing the device from the eye. The event was resolved within a week with no medical or surgical intervention. Six cases of subretinal fibrosis were reported of which three were attributed to the natural course of AMD, two were related to the vitrectomy procedure and one was thought to be related to the device. One case of RPE atrophy and a retinal tear were attributed to the device by the study investigator. The retinal tear was located peripheral to the macula and was treated with thermal laser with no complication.

One event of ocular hypertension was noted when a subject received an additional injection of Avastin[®] at a later follow up, which was thought to be related to the intravitreal injection procedure and resolved without sequelae.

Other adverse events reported in this study included 9 cases of reoccurrence of choroidal neovascularisation, 1 case of epiretinal membrane, 1 case of RPE detachment, 1 case of pre-retinal bleeding, 1 case of RPE hyperpigmentation, 1 case of conjunctivitis, 4 cases of moderate vision loss, 1 case of vitreous haemorrhage, 5 cases of cataract formation, 1 case of cystoids macular oedema, and 1 case of tubercular uveitis. The most frequently reported adverse event was reoccurrence of CNV, followed by 6 cases of subretinal fibrosis. Cataract formation was observed in five subjects which was not unexpected since vitrectomy has been shown to cause new cataracts, or accelerate cataractogenesis. Of the five patients affected by cataract formation, all of them elected to undergo phacoemulsification with intraocular lens placement. All of the surgeries were uneventful, with good clinical outcomes.

TABLE 6
OCULAR ADVERSE EVENTS
24 GY EPIRETINAL RADIATION + BEVACIZUMAB (N=34)

Adverse Event	Number of Events Reported	Worst Severity	Was this event Unanticipated
Cataract	5	Moderate	No
Cystoid Macular Oedema	1	Mild	No
Conjunctivitis	1	Moderate	No
Epiretinal Membrane	1	Moderate	No
Moderate Vision Loss (> lines vision loss)	4	Moderate	No
Ocular Hypertension	1	Severe	No
Tubercular Uveitis	1	Moderate	No
Pre retinal Blood	1	Mild	No
RPE Hyperpigmentation	1	Mild	No
Reoccurrence of CNV lesion	9	Moderate	No
RPE Detachment	1	Mild	No
Retinal Tear	1	Moderate	No
Subretinal Haemorrhage	1	Mild	No
Subretinal Fibrosis	6	Moderate	No
Vitreous Haemorrhage	1	Mild	No

Taken together, the results of NVI-111 and NVI-0068 suggest that 24 Gray offers a better outcome than 15 Gray, and that there is a synergistic effect when epimacular brachytherapy is combined with anti-VEGF therapy.

The CABERNET study is an international, multicentre randomised clinical trial of epimacular brachytherapy, given with a concomitant injection of Lucentis® at the time of surgery, and again one month later. Patients in the control arm receive three consecutive monthly injections of Lucentis® followed by repeat injections given every three months. Lucentis® retreatment is given to subjects in both arms if there is evidence of disease activity. The trial will follow up subjects for three years. Twelve month visual outcome data is expected to be reported in approximately November 2010. Adverse events reported to date in the CABERNET study show a favourable safety profile and the US Food and Drug Administration have approved an expansion of recruiting centres following initial safety analysis.

4.3 Study Rationale

Feasibility studies of the NeoVista® Ophthalmic System have shown the preliminary efficacy and safety of the treatment of subjects with subfoveal CNV secondary to AMD. The NeoVista® Ophthalmic System is currently under investigation in a randomised, prospective, active controlled, study (CABERNET) of treatment naïve subjects with subfoveal CNV secondary to AMD.

Although the current anti-VEGF therapy has proven effective in large clinical trials,^{11-15, 35} there are patients that do not achieve results that afford them a visual outcome that they, or their health care providers are satisfied with. There are a small number of patients that have a hypersensitivity reaction to Macugen®, Lucentis®, and Avastin® or any of the excipients involved in the formulations which exclude them from treatment with anti-VEGF therapy. There are patients that respond to anti-VEGF therapy, although the response is transient and requires continued injections over time. This can be burdensome for the subject from both a quality of life and financial standpoint. The long term effects of repeated intraocular injections as well as the long-term use of anti-VEGF therapy is not well understood in this patient population to date.

An uncontrolled, multicentre, Phase II study (MERITAGE) is underway to assess the effect of epimacular brachytherapy in patients who require frequent intravitreal injections to suppress disease activity. The current Phase III randomised clinical trial (MERLOT) is designed to demonstrate efficacy and safety of the VIDION® System for the treatment of patients with subfoveal CNV secondary to AMD who have commenced anti-VEGF therapy, and who might benefit from a treatment that has the potential to reduce their reliance on regular intravitreal injections. Previous epimacular brachytherapy studies (NVI-068, NVI-111 and CABERNET) have targeted treatment naïve patients, but MERITAGE and MERLOT aim to determine if previously treated patients (the largest group of patients with wet AMD), might also benefit from this device.

4.4 Risk vs. Benefits

The proposed patient population in this Investigational Study has been diagnosed and treated for CNV secondary to AMD and have commenced anti-VEGF therapy. Despite many patients benefitting from Lucentis®, 4-10% lose three lines of visual acuity,^{12,13,14} and NICE estimates that, on average, patients require eight intravitreal injections in the first year, six injections in the second, with ongoing lifelong injections thereafter. Many patients will require more frequent injections and all require monthly hospital review. Such an intensive dosing regimen represents a considerable burden on older patients, their carers, and the health economy. Repeated intravitreal injections carry a small but cumulative risk of complications including cataract, endophthalmitis, intraocular haemorrhage, retinal detachment, and systemic drug effects such as stroke. Further, the long term effects of Lucentis® are as yet unknown. A treatment that reduced the frequency of Lucentis® treatment would therefore benefit patients and the NHS.

The total risk to this subject population is both associated with the risk of the vitrectomy procedure and the delivery of ionising radiation.

Partial pars plana vitrectomy required for use of the VIDION® System has risks including retinal detachment, development of cataract, and haemorrhage and/or infection within the eye including endophthalmitis. In the feasibility studies of the use of the NeoVista® device there have been no reported cases of endophthalmitis with the treatment of 90 subjects, although a recent case of non-infectious endophthalmitis has been reported in the CABERNET study. Additional risks include corneal abrasion, tearing of the retina, loss of depth perception, blurring of vision, double vision, or blindness, and cystoid macular oedema or loss of the eye, an event that is extremely rare. Minor side effects could include discomfort from the procedure.

The risks of vitrectomy have been mitigated by the use of a validated cleaning and sterilisation protocol for the device, as well as an extensive surgical training program for the surgeons and surgical staff involved in the study. The training program involves the

use of a model eye and a replica VIDION[®] device that allows the surgeon to practice placement of the device in the intraocular compartment.

There are risks involved with delivering radiation directly to the retina using the VIDION[®] device. Sight threatening side effects include damage to the optic nerve, retina, and choroid and treatment may cause cataract or glaucoma. It is also possible that “radiation retinopathy” could occur.

The risks of radiation delivery have been mitigated by the design of the VIDION[®] device. The design is optimised to deliver radiation to the diseased tissue and at the same time minimise exposure to other healthy ocular tissues. Strontium-90 has been chosen as the isotope of choice with the VIDION[®] Ophthalmic System based upon its favourable radioactive characteristics. It is well suited to treat a disease such as AMD within the intraocular compartment due to its relatively shallow penetration of tissue, and the rapid reduction as a function of distance from the source. Strontium-90 has the ability to be safely shielded when not in use and the ability to deliver a therapeutic dose in a short period of time. These characteristics make this isotope the most appropriate choice for use within the VIDION[®] Ophthalmic System to treat AMD.

Loss of vision often leads to loss of independence and to a lowered self-esteem, which can be stressful for patients and their families. Visual impairment can decrease mobility, increase the risk of injury caused by falls, and result in emotional distress and depression. Based on data in treatment naïve patients (NVI-111) it is predicted that the VIDION[®] device will decrease the number of intravitreal injections that the patient has to receive, and that vision will be similar to treatment with Lucentis[®].

Thus, in the study population of patients with active choroidal neovascularisation, who require ongoing therapy with Lucentis[®], the potential benefit of radiation therapy in reducing the number of intravitreal injections whilst maintaining vision outweighs the risks.

5 INVESTIGATIONAL PLAN

5.1 Trial Design

The MERLOT Trial is a multi-centre, randomised, controlled clinical study of the VIDION[®] System for the treatment of subfoveal CNV associated with wet AMD in patients who have been previously treated with Lucentis[®]. It is designed to test the hypothesis that epimacular brachytherapy will reduce the frequency of Lucentis[®] re-treatment that patients require, whilst maintaining visual acuity.

A total of 363 patients who are receiving regular Lucentis[®] treatment will be randomised in a 2:1 ratio to Arm A or Arm B:

Arm A: A single surgical procedure with epimacular brachytherapy using the VIDION[®] System, with Lucentis[®] (0.5 mg) administered on a monthly basis as required, using the re-treatment criteria below.

Arm B: Lucentis[®] (0.5 mg) administered on a monthly basis as required, using the re-treatment criteria below

Both groups will receive ongoing Lucentis[®] treatment administered as required, based on pre-defined retreatment criteria.

The trial will enrol across approximately 35 sites.

The MERLOT trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and all of the applicable regulatory requirements.

5.2 Study Objective

The objective of the MERLOT Trial is to evaluate the safety and efficacy of focal delivery of radiation for the treatment of subfoveal CNV associated with established wet AMD previously treated with anti-VEGF therapy.

5.3 Safety Parameters

Safety parameters to be evaluated include incidence and severity of adverse events and ocular adverse events identified by eye examination. This will include the incidence of cataract changes and the incidence of radiation induced toxicity.

5.3.1 Radiation Retinopathy

Radiation toxicity to the retina and ocular structures will be monitored throughout this study by both the Chief Investigator, and Principal Investigators at each site. Radiation retinopathy is well described in the literature and typically occurs between 6 months and 3 years.³⁷ The most common clinical signs associated with “radiation retinopathy” are:

- Retinal Oedema
- “Ghost Vessels” caused by vascular lumen closure
- Cotton wools spots
- Vascular sheathing
- Microaneurysm formation
- Intraretinal haemorrhage
- Telangectasias
- Neovascularisation

Many of these clinical signs are also associated with the natural progression of AMD and should be followed carefully and documented as adverse events as per Section 10 of this protocol.

5.4 Efficacy Parameters

The co-primary outcome measures of efficacy are:

1. Mean change in ETDRS best-corrected visual acuity.
2. The mean number of re-treatment injections of Lucentis[®] per patient, per year.

Secondary efficacy parameters that will be assessed will be the following:

- Percentage of subjects losing < 15 ETDRS letters
- Percentage of subjects gaining ≥ 0 ETDRS letters
- Percentage of subjects gaining ≥ 15 ETDRS letters
- Change in total lesion size by fluorescein angiography
- Change in total CNV size by fluorescein angiography
- Foveal thickness measured using OCT.

5.5 Subject Population

The population to be studied will be comprised of 363 men and women ≥ 50 years of age with a diagnosis of subfoveal choroidal neovascularisation associated with wet age-related macular degeneration, who have commenced treatment with intravitreal Lucentis® in accordance with NICE guidance. It is anticipated that subjects will have been referred for treatment with epimacular brachytherapy by their treating ophthalmologist, or be under the care of the Investigator prior to screening. Patients may also contact study sites after seeing the study website (www.merlotstudy.com). This has information for both health professionals and patients who may be interested in the trial and contains the contact details for their local participating hospital.

Subjects must have met all eligibility criteria stated in 5.5.1 and 5.5.2.

The eligibility criteria are:

5.5.1 Informed Consent

Only subjects who have provided informed consent, including signing of the ethics committee approved informed consent form, are eligible for screening.

5.5.2 Subject Screening

5.5.2.1 Inclusion Criteria

1. Subjects with subfoveal choroidal neovascularisation associated with wet age-related macular degeneration. Retinal Angiomatous Proliferation (RAP) lesions

-
- not directly involving the fovea must be associated with contiguous foveal leakage demonstrated on fundus examination, OCT, or fluorescein angiography;
2. Subjects must have received anti-VEGF induction treatment, defined as the first three months of anti-VEGF therapy. Following this induction period, subjects must have received at least 4 additional injections of Lucentis[®] in no more than 12 months preceding enrolment, or 2 additional injections of Lucentis[®] in no more than 6 months preceding enrolment, given on an as needed basis Please see figure below. For patients who have received both Avastin[®] and Lucentis[®] prior to enrolment please see the note at the end of this section;
 3. At the time subjects commenced anti-VEGF therapy for wet age-related macular degeneration they were aged 50 years or older and met the NICE treatment criteria for Lucentis[®] therapy, as outlined in the Final Appraisal Determination (FAD). This states that all of the following circumstances must apply in the eye to be treated:
 - the best-corrected visual acuity is between 6/12 and 6/96 (24 to 69 ETDRS letters)
 - there is no permanent structural damage to the central fovea
 - the lesion size is less than or equal to 12 disc areas in greatest linear dimension
 - there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes)

If more than one eye is eligible the patient may choose which eye they wish to have allocated as the study eye. The clinician should discuss all relevant clinical issues to help the patient make an informed decision. This discussion might consider issues such as the lens status, clinical response to ranibizumab, risk factors, visual acuity and visual potential.

The following figure demonstrate the inclusion criteria for injection requirements

Option 1

2 additional LUCENTIS injections in 6 months preceding enrolment



Option 2

4 additional LUCENTIS injections in 12 months preceding enrolment



X = any interval (including 0 months) between induction and assessment of LUCENTIS (ranibizumab) retreatment requirements.

Note that patients *may* be eligible for inclusion if they have received both Avastin[®] and Lucentis[®]. This is because inclusion Criteria 2 does not specify which anti-VEGF agent is used for induction treatment. Therefore induction treatment may have been undertaken with Avastin[®], Macugen[®] or Lucentis[®]. It does however require patients to have received a certain minimum number of Lucentis[®] injections, given ‘as required’, in the 6 or 12 months prior to enrolment. Therefore, as an example, a patient may have received induction with Avastin[®], and further maintenance (‘as required’) Avastin[®] injections, after which time he or she was changed to Lucentis[®] treatment. Provided the requisite number of ‘as required’ Lucentis injections were administered prior to enrolment the patient would be eligible. By contrast, if the patient had only ever been treated with Avastin[®] they would not be eligible.

5.5.2.2 Exclusion Criteria

1. Patients who have not been treated in accordance with NICE guidance;
2. Visual acuity worse than 6/96 (24 ETDRS letters) at the time of study enrolment;
3. Subjects with prior or concurrent subfoveal CNV therapy with agents, surgery or devices (other than Macugen[®], Avastin[®], or Lucentis[®]) including thermal laser photocoagulation (with or without photographic evidence), photodynamic therapy, intravitreal or subretinal steroids, and transpupillary thermotherapy (TTT);
4. Subfoveal scarring;
5. Subjects with active concomitant disease in the study eye, including uveitis, presence of pigment epithelial tears or rips, acute ocular or periocular infection;
6. Subjects who have been previously diagnosed with Type 1 or Type 2 Diabetes Mellitus. Subjects who do not have a documented diagnosis, but have retinal findings consistent with Type 1 or Type 2 Diabetes Mellitus;
7. Subjects with advanced glaucoma (greater than 0.8 cup:disk) or intraocular pressure ≥ 30 mmHg in the study eye;
8. Previous glaucoma filtering surgery in the study eye;
9. Subjects with inadequate pupillary dilation or significant media opacities in the study eye, including cataract, which may interfere with visual acuity or the evaluation of the posterior segment;
10. Current vitreous haemorrhage in the study eye;
11. History of rhegmatogenous retinal detachment or macular hole in the study eye;
12. Subjects who present with CNV due to causes other than AMD, including subjects with known or suspected idiopathic polypoidal choroidal vasculopathy (IPCV), ocular histoplasmosis syndrome, angioid streaks, multifocal choroiditis, choroidal rupture, or pathologic myopia (spherical equivalent ≥ 8 Dioptre or axial length ≥ 25 mm);

-
13. Subjects who have undergone any intraocular surgery in the study eye within 12 weeks prior to the screening visit, with the exception of cataract surgery as discussed in the Exclusion Criteria #14;
 14. Previous cataract surgery within 2 months prior to enrolment into the study;
 15. Subjects with known serious allergies to fluorescein dye used in angiography;
 16. Subjects with known sensitivity or allergy to Lucentis®;
 17. Subjects who underwent previous radiation therapy to the eye, head or neck;
 18. Subjects with an intravitreal device or drug in the study eye;
 19. Subjects with any other condition, which in the judgment of the investigator would prevent the subject from completing the study (e.g. documented diagnosis of dementia or serious mental illness);
 20. Current participation in another drug or device clinical trial, or participation in such a clinical trial within the last year;
 21. History of use of drugs with known retinal toxicity, including: chloroquine (Aralen – an anti-malarial drug), hydroxychloriquine (Plaquenil), phenothiazines, chlorpromazine (Thorazine), thioridazine (Mellaril), fluphenazine (Prolixin), perphenazine (Trilafon), and trifluoperazine (Stelazine);
 22. Subjects who are unwilling or unable to return for scheduled treatment and follow-up examinations for three years;
 23. Women must be post-menopausal ≥ 1 year unless surgically sterilised.

6 STUDY PROCEDURES BY VISIT

The study procedures by visit are outlined in the table that follows. The procedure to be followed for Informed Consent, treatment using the Vidion® system, and administration of Lucentis® are detailed elsewhere in the protocol (see Section 8). Slit lamp anterior segment examination, biomicroscopic fundus examination, and measurement of intraocular pressure (IOP) are standard clinical techniques. ETDRS visual acuity, fundus photography and optical coherence tomography are described in Section 9.

6.1 Cataract assessment and surgery

Visually significant cataract will interfere with assessment of visual acuity and macular function. It is important that investigators make a careful assessment of lens clarity during screening, to exclude patients in either group who have visually significant cataract.

Cataract is a relatively common side effect of vitrectomy. A Phase II study of epimacular brachytherapy³⁴ suggests that visually significant cataract develops in approximately 25% of eyes within 12 months of surgery. A much lower percentage of eyes in the Lucentis® monotherapy group are likely to develop cataract over this timeframe. It is important that any visually significant cataract is treated prior to the key milestones for data collection at Month 12 and 24.

There are three types of cataract assessment in this study:

- A monthly, unmasked review to determine if visually significant cataract is present or absent;
- A more formal but unmasked assessment using the LOCSII system to grade lens opacity at key milestones (Screening and Month 12, 24, and 36);
- Four masked cataract assessments using the LOCSII system to ensure that cataracts are treated in a timely manner. Additional masked cataract assessments may also be required if cataract develops in between these four visits.

Masked cataract assessment: A masked assessment of lens opacity must be undertaken at Month 6, 9, 18, and 21 in both subjects and controls, if the study eye is phakic. If the study eye is pseudophakic then masked cataract assessment is not required in either eye. Lens opacity will be graded using the LOCSII system, shown in Appendix 2. Masked cataract assessment should be undertaken by a Cataract Assessor who is masked to treatment allocation. The Cataract Assessor must be an Ophthalmologist who has undertaken at least 400 phacoemulsification cataract operations. To maintain masking the Masked Cataract Assessor should determine the degree of cataract without inspection of the vitreous cavity. The Cataract Assessor should examine the study eye lens prior to

assessment of the fellow eye, so that any asymmetry in the degree of lens opacity does not lead the Assessor to conclude that this is due to vitrectomy, preventing masked assessment.

Cataract grading at Screening, Month 12, 24, and 36: An unmasked LOCS II grading of the lens opacity is undertaken at Screening, and yearly thereafter. This should occur in both the study eye and fellow eye. If a participant is, or becomes, pseudophakic in an eye then LOCSII cataract assessment is not required in that eye, other than to record that the eye is pseudophakic.

Monthly cataract assessment: In addition to the above masked LOCSII assessment of cataracts, a non-masked assessment is undertaken at each monthly visit, to determine if visually significant cataract is present or absent. If visually significant cataract develops at these time points, then the subject should be referred for masked cataract assessment as outlined above.

Cataract Surgery: If cataract surgery is deemed appropriate then this should be undertaken at least four weeks prior to the end of year visit. Cataract surgery should be undertaken by an Ophthalmologist who has undertaken at least 400 phacoemulsification cataract operations.

6.2 Screening

Before subjects undergo formal screening they must have provided written informed consent. Once the screening process has commenced, then baseline treatment must be undertaken within 21 days. Once screening is complete, and if subjects are eligible for inclusion, then randomisation is undertaken. Subjects may have screening, randomisation and baseline treatment on the same day. It is anticipated that in most cases the screening visit will be undertaken on one day, but the subject may return for a subsequent visit if this is necessary to complete all the requisite tests, or the subject would prefer to have the

tests split over two visits. However, screening will preferably be completed within one week, and must not extend for more than 21 days.

An electronic randomisation system is incorporated in the electronic CRF system. The patient will be allocated to treatment Arm A or Arm B, once the inclusion and exclusion criteria have been entered, and it has been determined that the patient is eligible for enrolment. Randomisation is stratified, as detailed in Section 11.1. A patient study identification card will be provided to the patient to carry around with them while they are in the study. A template will be supplied to each site, which can be modified with local contact details.

6.3 Baseline

Subjects randomised to treatment with epimacular brachytherapy (Arm A) will undergo surgery within 21 days of the start of the screening process.

Lucentis® should be administered at baseline if the retreatment criteria are fulfilled. Section 7.7 details the retreatment criteria and how these should be applied to subjects who have just entered the study.

If subjects in Arm A require Lucentis® at baseline, this should not be administered until the end of their operation, to avoid removal of intravitreal Lucentis® during the course of the vitrectomy.

If subjects in Arm B (control) require Lucentis® at baseline, this should be administered within 21 days of the start of the screening process. As noted above, the screening visit and baseline treatment can occur on the same day. Therefore if the screening assessment determines that a subject in Arm B requires baseline Lucentis®, this can be administered the same day (but no more than 21 days after the start of screening). If the screening visit determines that a subject in Arm B does not require Lucentis, then the subject does not need to return for review until the Month 1 visit, and the screening visit and baseline visit

will be taken to have occurred on the same day. The technique for administering Lucentis® is detailed in Section 8.

6.4 Monthly Subject Visits

After enrolment, subjects will be followed monthly (28 days \pm 7days) as specified in the MERLOT Study visit schedule (see Section 6.6). The visits will be monthly for 24 months to reach the primary endpoints. There will be a final visit 12 months later (36 month) to further evaluate the safety parameters as specified in Section 5 and the number of injections they have received since the 24 month visit as recorded in their clinical notes.

Between the 24 month and the 36 month visit, the subject will return to their NHS clinic, where there will be no data collection for the study.

Sites will be provided with a spreadsheet program so the patient visit schedule can be easily calculated and the visit windows are clearly stated.

6.5 Health Economic Questionnaires

Patient questionnaires will be administered to determine if epimacular brachytherapy provides value for money and produces an improvement in patients' quality of life. Subjects will complete the National Eye Institute (NEI) 25-Item Visual Function Questionnaire (VFQ-25) and Health Utilities Index questionnaire (HUI[®]) questionnaires at enrolment, Month 3, 6, 12, 18 and 24. The correct method for administering the questionnaires is outlined in Appendix V and VI. Large print versions of both questionnaires are available in the source documents.

While there is overlap between the HUI[®] and NEI VFQ-25 questionnaires, using the NEI VFQ-25 (as well as the HUI[®]) has the advantage that the study can compare VFQ-25 results for this trial population to those reported for other trials. This provides some indication of the baseline quality of life (in terms of visual function) and a change in response to treatment of the population compared on a common scale with other trial populations.

The above two considerations mean the MERLOT study has the ability to compare (in terms of vision) against other trials and within the trial, based on a widely-used and widely reported vision specific measure. It will also produce an accepted, generic quality of life measure that has been shown to be sensitive to change, in populations with visual impairment. The added advantage of the HUI[®] is that it can also be readily scored to produce utility values.

Responses to a generic health-related quality of life instrument (Health Utilities Index, HUI-3), chosen due to its demonstrated performance in discriminating quality of life differences by visual acuity in UK population will be valued using a standard tariff.³⁸ These values will be used to derive QALYs associated with each arm in the trial.

6.6 Merlot Visit Schedule

MERLOT STUDY YEAR 1 SCHEDULE OF PARAMETERS AND VISITS

	Screening	Baseline	Day 1	Week 1	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Visit window	Day -21 to 0	Day 0	Day 1	±3 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days
Informed consent	X															
Randomisation	X															
Ophthalmic History	X															
Arm A (VIDION™)		X ¹			X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹
Arm B (Lucentis® monotherapy)		X ¹			X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹
Slit Lamp Anterior	X		x ²	x ²	X	x	x	x	x	C	x	x	C	x	x	X
Fundus Examination	X	X	x ²	x ²	X	x	x	x	x	X	x	x	x	x	x	X
IOP	X		x ²	x ²	X	x	x			X						X
Manifest Refraction	X				X	X	X	X	X	X	X	X	X	X	X	X
BCVA (ETDRS)	X		x ²	x ²	X	X	X	X	X	X	X	X	X	X	X	X
VFQ-25	X						X			X						X

HUI	X							X			X						X
FFA	X																X
Colour fundus Photography	X																X
OCT (read centrally)	X																X
OCT (foveal thickness)	X				X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X ²	X ²	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X ²	X ²	X	X	X	X	X	X	X	X	X	X	X	X	X

X¹ Lucentis administered on an as required basis, using re-treatment criteria given in protocol. X²: Vidion (Arm A) only. Points marked with a gray lowercase 'x' indicate that test should be recorded as having been completed, but data sent centrally only if abnormal or adverse outcome. Data collection in study eye only, except at screening visit. C: Subjects and controls should be assessed for the presence of cataract in the study eye. This assessment should be undertaken by a masked assessor, as detailed in Section 6.1. If significant cataract is evident then cataract surgery should be undertaken at least 4 weeks prior to the 12 month visit. If significant cataract develops at other visits this should also be assessed by a masked assessor.

MERLOT STUDY YEAR 2 AND 3 SCHEDULE OF PARAMETERS AND VISITS

	Month 13	Month 14	Month 15	Month 16	Month 17	Month 18	Month 19	Month 20	Month 21	Month 22	Month 23	Month 24	Month 36
Visit window	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±14 days
Informed Consent													
Randomisation													
Ophthalmic History													
Arm A (VIDION™)	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹
Arm B (Lucentis® monotherapy)	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹	X ¹
Slit Lamp Anterior Segment Examination	x	x	x	x	x	C	x	x	C	x	x	X	X
Fundus Examination	x	x	x	x	x	X	x	x	x	x	x	X	X
IOP						X						X	X
Manifest Refraction	X	X	X	X	X	X	X	X	X	X	X	X	X
BCVA (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X
VFQ-25						X						X	
HUI						X						X	
FFA												X	
Colour Fundus Photography												X	
OCT (read centrally)												X	
OCT (foveal thickness)	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X

X¹ Lucentis® administered on an as required basis, using re-treatment criteria given in protocol. Points marked with a gray lowercase x indicate that test should be recorded as having been completed, but data sent centrally only if abnormal or adverse outcome. Data collection in study eye only except at screening visit. C: Subjects and controls should be assessed for the presence of cataract in the study eye. This assessment should be undertaken by a masked assessor, as detailed in Section 6.1. If significant cataract is evident then cataract surgery should be undertaken at least 4 weeks prior to the 24 month visit. If significant cataract develops at other visits this should also be assessed by a masked assessor.

7 STUDY CONDUCT

7.1 Investigator Responsibility

Approximately thirty five clinical centres will participate in this trial. Investigators must comply with the signed Sponsor-Site Agreement.

7.2 Radiation Licensing/Certification

All sites participating in this study will have attained the appropriate national and local licensing requirements to allow for the utilisation of the VIDION[®] System at the participating institution. All sites will have obtained licenses to administer epimacular brachytherapy, and to store the Strontium-90 device, in accordance with the requirements of the Administration of Radioactive Substances Advisory Committee (ARSAC) and the Environment Agency. Each clinical site will provide proof of documentation of the licensure to the Sponsor prior to the enrolment of any subjects in this study.

A Radiation Safety Officer (RSO) or Medical Physicist will be involved in the oversight of the radiation handling and storage at each site, and a named individual will be identified to the sponsor.

A named clinical radiation expert, such as a Radiation Oncologist or Nuclear Medicine Consultant, will oversee the delivery of radiation treatment at each site. A named individual taking overall responsibility for the delivery of epimacular brachytherapy will be identified to the sponsor. A clinical radiation expert must be present in theatre for the first three epimacular brachytherapy cases treated by each surgeon. Thereafter the clinical radiation expert may decide not to attend theatre during the delivery of epimacular brachytherapy, if this is in accordance with current national and local regulations, but he or she retains responsibility for the delivery of radiation treatment.

The sponsor has a senior radiation safety advisor who is available to answer questions relating to epimacular brachytherapy. Please contact:

Cornelius Lewis

Director of Medical Engineering and Physics
King's College Hospital
London SE5 9RS

Tel: 020 3299 1610

Email: cornelius.lewis@kch.nhs.uk

7.3 Regulatory Authority and Ethics Committee Approval

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

The protocol and related documents will be submitted for review to the South West Research Ethics Committee (REC)(Research Ethics Service, Royal Devon and Exeter Hospital, Gladstone Road, Exeter, EX1 2ED), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

Annual progress and safety reports and a final report at conclusion of the trial will be submitted to the JCTO (on behalf of the Sponsor), the REC and the MHRA within the timelines defined in the Regulations.

Prior to recruitment of any subjects into the study at each participating site, Site Specific Approval (SSA) and NHS Research and Development approval must also be obtained.

7.4 Subject Identification Number

Once a subject has provided informed consent, including signing the informed consent form, a Subject Identification (ID) Number will be assigned. The first three digits of the ID number will be the site number followed by a three-digit number in sequential order (i.e., 123001, 123002, 123003 etc.). This ID number will be retained throughout the study.

The ID number and subject initials are to be recorded on all study documents and will link the study treatment and the study documents to the subject's name and medical record. To maintain confidentiality, the subject's name should not be recorded on any study document other than the informed consent form and the Subject ID log. Subjects who withdraw from the study will not be replaced. (see Section 7.7)

7.5 Screen Failures

Screen Failures will be captured on the screening/enrolment form. The following minimum information will be collected on all screen failures- ID, subject initials, date of screening visit, reason for screen failure.

7.6 Protocol Deviations

Except to protect the life or physical well-being of the subject in an emergency, the investigator may not deviate from the protocol.

If the investigator deviates from the protocol in the case of such an emergency, the investigator must notify the sponsor and the reviewing Ethics Committee and/or the MHRA as soon as possible but no later than 3 working days.

Other than the emergency protocol deviations described above, the investigator must obtain advance sponsor approval for any other protocol deviations and changes to the investigational plan. If the proposed protocol deviations or changes to the protocol may affect the scientific soundness of the plan, or the rights, safety, or welfare of human subjects, they must also be approved in advance by the Ethics Committee and/or the MHRA.

7.7 Re-Treatment Criteria

Lucentis[®] should be administered if any of the following four conditions are met:

- The subject has lost more than five letters of visual acuity from baseline, and this is attributable to active wet AMD;
- An increase of more than 50 microns in central retinal thickness from the lowest central retinal thickness measurement secondary to new or increased subretinal, intraretinal, or sub-RPE fluid, as confirmed by OCT;
- Presence of new, or an increase from the last visit in subretinal or intraretinal blood;
- New neovascularisation as confirmed by fluorescein angiography.

The observations that are used to determine if retreatment should occur are only those made during the subject's participation in the trial. For example, to determine if there has been a 50 micron increase in OCT thickness the current measurement should be compared to the lowest OCT measurement acquired during the subject's participation in the trial - it should not be compared to any pretrial OCTs. The exception to this rule is observations made at Baseline/Screening, as there are no prior trial observations to use for retreatment decisions. At the Baseline/Screening visit, observations should be compared to recent pretrial clinical observations, but the above retreatment criteria still apply. If the retreatment criteria apply at Baseline, then Lucentis[®] should be administered for subjects in both Arm A (VIDION[®]) and Arm B (Lucentis[®] monotherapy). Baseline treatment with Lucentis[®] in Arm A can be given concomitantly at the end of surgery, as detailed in Section 8.2.10 or given up to 21 days from the Screening visit.

The technique for OCT analysis is given in Section 9.3.

If the treating ophthalmologist decides that Lucentis[®] re-treatment would be beneficial for persisting subretinal, intraretinal, or sub-RPE fluid confirmed on OCT, but the re-treatment criteria are not fulfilled, then he or she may administer Lucentis[®], but this should be recorded as a deviation.

If the eye does not show a decrease in fluid after three consecutive monthly injections, the treating ophthalmologist may choose to suspend treatment. Treatment may be re-initiated if the subretinal, intraretinal, or sub-RPE fluid becomes worse (relative to the visit when treatment was suspended) on OCT. Additional therapy will be recorded in the CRFs.

7.8 Withdrawal

Subjects have the right to withdraw from the study at any time, for any reason, without jeopardising their medical care. If a subject who has been enrolled into the trial withdraws from the study or is withdrawn from the study by the investigator before they receive their treatment, withdrawal must be immediately documented on the withdrawal CRF.

The investigator may withdraw subjects from the study, using the following criteria in determining whether to do so:

- Withdrawal of subject informed consent;
- Intercurrent illness that prevents continuation of regular follow-up visits;
- Unacceptable toxicity or allergy as judged by the investigator;

Any subject who withdraws from the study or whom the Investigator withdraws from the study will not be eligible for further treatments but must be asked to return to the clinic for an early withdrawal visit. At the withdrawal visit the subject will have the following procedures performed:

- Manifest refraction
- BCVA (ETDRS)
- SLE
- IOE
- IOP
- Record adverse events
- Record concomitant medications/procedure related meds
- FA
- Colour fundus photography
- OCT

Subjects who withdraw from the study or whom the investigator withdraws from the study should be encouraged to return for safety follow-up, at least every three months, until Month 24. Also, subjects who withdraw or are withdrawn because of an adverse event should be encouraged to return for follow-up of the AE until resolution or stabilisation of the adverse event. Subjects who withdraw from the study will not be replaced.

8 DESCRIPTION OF INVESTIGATIONAL INTERVENTION

8.1 Lucentis® Therapy

Subjects who enrol on this study will already be receiving regular intravitreal therapy with Lucentis® (ranibizumab). Both subjects and controls will continue to receive ‘as required’ Lucentis®, based on predefined re-treatment criteria that are given in Section 7.7. These re-treatment criteria mirror standard practice.

Lucentis® is a recombinant monoclonal antibody fragment that targets vascular endothelial growth factor A (VEGF-A). Lucentis® is indicated for the treatment of neovascular AMD and comes prepared as a solution for intravitreal injection. NICE guidance recommends that treatment is commenced as three consecutive monthly intravitreal injections. Following this three month loading dose, NICE recommends ‘as required’ monthly injections, if there is evidence of disease activity. Administration of Lucentis® will be as recommended by the manufacturer, in accordance with the summary of product characteristics (SPC). The SPC states that:

“Lucentis must be administered by a qualified ophthalmologist experienced in intravitreal injections....”

“As with all medicinal products for parenteral use, Lucentis® should be inspected visually for particulate matter and discoloration prior to administration.”

“The injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent) and the availability of sterile paracentesis (if required)”

“The periocular skin, eyelid and ocular surface should be disinfected and adequate anaesthesia and a broad-spectrum topical microbicide should be administered prior to the injection”.

“The injection needle should be inserted 3.5 – 4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 ml is then delivered; a different scleral site should be used for subsequent injections.”

“...any unused product or waste material should be disposed of in accordance with local requirements”

The marketing authorisation holder for Lucentis is Novartis Europharm Ltd., Wimblehurst Road, Horsham, West Sussex, RH12 5AB. The product code is eu/1/06/374/001. The SPC is available at <http://emc.medicines.org.uk> .

Hospital Lucentis stock will be used for both arms of this study and will be labelled according to regulatory requirements prior to dispensing. Return and destruction of Lucentis must be documented. Storage conditions and full accountability must be maintained by pharmacy staff at each site and will be reviewed by the sponsor’s representatives.

8.2 VIDION[®] System

The VIDION[®] system is intended for use in ophthalmic surgery for the treatment of patients with CNV secondary to AMD. It delivers 24 Gray of beta radiation to the CNV lesion. The device comprises a reusable housing containing the radioactive source (Strontium-90), and a disposable component that comprises a remote handpiece to activate the device and an intraocular probe to deliver the radiation source into the eye. An image of the device, and device description, is given in Section 2. The generic name for the intervention is epimacular brachytherapy. Epimacular brachytherapy requires the subject to first undergo pars plana vitrectomy.

The device is manufactured by NeoVista Inc, 47865 Fremont Blvd, Fremont, CA 94538, USA, Telephone +1 510 933 7600, Fax +1 510 933 7659, Email info@neovistainc.com. The CE mark is anticipated to be obtained June 2009. The study will not commence until the CE mark is obtained. The VIDION[®] system is distributed in the UK by Carlton Ltd, Pattison House, Addison Rd, Chesham, HP5 2PD; Telephone 01494 775811; Fax 01494 774371; Email carleton@carletonltd.com.

The VIDION[®] operator’s manual is provided in Appendix 1.

8.2.1 Preparation of the VIDION[®] System

The disposable components of the Vidion[®] System will be provided in single-use sterile packs. The re-useable radiation delivery module must be sterilized and tested as instructed in the Vidion[®] System Operator's Manual.

8.2.2 Radiation Monitoring

Appropriate radiation monitoring of the subject, surgeon, and assistant during VIDION[®] System delivery is recommended as specified by the national and local regulations as well as the RSO at the participating institution.

8.2.3 Device Malfunction

A device malfunction is defined as a failure of the device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in this protocol, the VIDION[®] System Operators Manual, or the product associated labelling included with the device. Examples of malfunctions could include:

- Missing product components;
- Missing or illegible product associated labelling;
- Devices which appear malformed or disfigured;

All device malfunctions will be reported to the device manufacturer NeoVista by fax (001 510-279-5529), e-mail (safety@neovistainc.com), or phone (001 510-933-7600) as per the VIDION[®] System Operators Manual, and to the Chief Investigator. Local reporting guidelines will also be followed, including documentation of an adverse event involving a medical device.

8.2.4 Anaesthesia

Surgery may be performed using either peribulbar or subtenon anaesthesia. The surgeon, in consultation with the anaesthetist may use general anaesthesia (example, propofol) for certain subjects allowing for appropriate cardiac and respiratory monitoring.

All medications delivered to the subject during the surgical procedure will be documented on the appropriate source documents and transferred to the CRFs.

8.2.5 Pretreatment Planning

Prior to treatment, the surgeon will confirm the location of the lesion using retinal vascular landmarks. The preferred location of the sclerotomy entry point will be identified (i.e., temporal, nasal, and specific clock hour) to provide limited exposure of the fovea and optic nerve during treatment. It is recommended that the surgeon have a representative fluorescein angiogram or colour fundus photograph within view at the time of surgery to aid in the localisation of the lesion during the procedure.

8.2.6 Vitrectomy Procedure

A speculum will be placed in the lid and the surgery will begin with a conjunctival incision in the superotemporal, superonasal and inferotemporal quadrants. If performing 25 gauge or 23 gauge surgery, it is recommended to displace the conjunctiva toward the corneal limbus, which will allow for mis-alignment of the conjunctival and scleral incisions reducing the direct pathway for pathogen entry into the globe. A scleral incision will be made at 3-4 mm away from the corneal limbus and an infusion cannula will be inserted into the vitreous cavity. The location of this sclerotomy must be documented on the source documents and CRFs for every case. After confirming that the infusion cannula is in its appropriate positioning, the infusion line is opened and a second and third sclerotomy will be created at 3-4 mm away from the corneal limbus in the location determined during pretreatment planning. These locations must be documented on the source documents and CRFs for every case. For vitrectomy performed with 23 and 25 gauge systems, the third port should be enlarged to accommodate the placement of the 20 gauge NeoVista® Ophthalmic System.

An appropriate lens for vitreoretinal surgery will be placed. It is recommended to use a wide field corneal lens with magnification of the microscope at medium magnification to allow for the best field of view when placing the probe, but the lens choice will be at the discretion of the operating surgeon and can include non-contact systems.

A standard endoilluminator will be used to illuminate the vitreous cavity.

A standard “full” (rather than core) pars plana vitrectomy will be performed to allow for placement of the VIDION® System directly above the lesion as described in 8.2.6.

It is important to perform a careful, 360 degree, indented , internal examination of the peripheral retina after epimacular brachytherapy has been delivered. Treatment of any peripheral breaks should be performed with laser or cryotherapy to prevent subsequent retinal detachment. Air or gas tamponade should be injected if required.

8.2.7 Radiation Delivery

Using the landmarks identified in pretreatment planning, the centre marker (“cross hairs”) on the tip of the delivery probe will be positioned directly above the centre of the CNV complex. For large lesions, the probe should be centred over the lesion, but no more than 2 mm away from the edge of the lesion that involves the macula. Once the anatomic landmarks for positioning the device are located, the surgeon moves the probe into the mid vitreous cavity. The surgeon instructs the assistant to engage the device, allowing the source to travel to the tip of the cannula. The surgeon then brings the probe into gentle contact with the retina and the timer is started. The prescribed radiation dose of 24 Gy will then be delivered by monitoring the precise amount of time the radiation source resides at the treatment site. [Refer to VIDION[®] System Operators Manual for calculation of treatment time]. The treatment time can be found on the Certificate of Calibration that comes with each device. The weight of the device is fully supported by the surgeon’s hand, and contact with the retina will be as light as possible. Appropriate hand and wrist support must be available. Light contact with the retina will result in an appropriate distance from the surface of the probe to the treatment area (Figure 6).

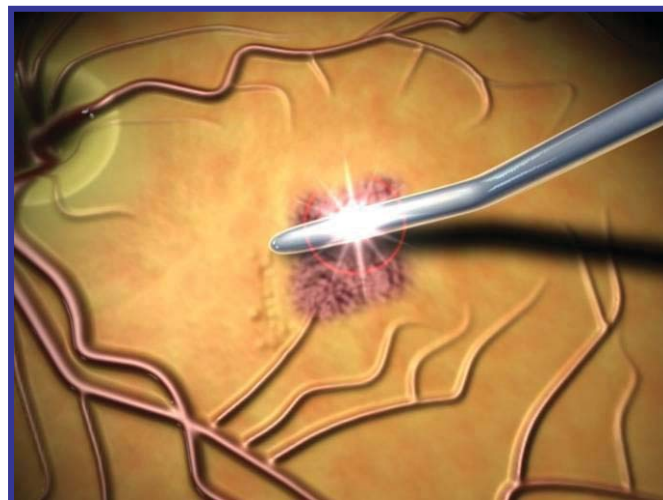


FIGURE 6. RADIATION DELIVERY PROBE IN POSITION (COURTESY NEOVISTA INC)

8.2.8 Treatment Time

The treatment time for radiation delivery is determined from previous calibration of the device and explained in detail in the VIDION[®] System Operators Manual. The start time must not be initiated while the device is in the mid-vitreous cavity. The supplied timer must be started once the radiation source has been engaged and is in position on the retina. Due to the delicate nature of the procedure and the need to keep the probe steady, the operating suite should be as quiet as possible to allow for Investigator concentration. The personnel responsible for timing the procedure should call out the remaining time every 30 seconds to a minute to let the Investigator and operating room staff know how much time remains. The treatment time must be recorded on the source documents and the corresponding CRF.

8.2.9 Probe Removal

After the prescribed radiation dose is delivered, the probe tip will be moved to the mid-vitreous cavity, the source will be retracted, and the delivery probe will be removed from the eye.

8.2.10 Injection of Lucentis[®] Therapy After Radiation delivery

Once the probe is removed, a single injection of Lucentis[®] therapy (if applicable according to Section 7.7) is to be given intraocularly per prescribing instructions and Section 8.1/8.2. If the 25/23 gauge sclerotomy holes will be left open with no closure, it is important to deliver the injection of Lucentis[®] at a location that is distant to these open ports to eliminate the possibility of drug reflux.

8.2.11 Closure

The superior sclerotomies will be closed with ophthalmic sutures (if necessary) and the infusion cannula will be removed. After closure of the infusion sclerotomy, the conjunctiva will also be sutured with appropriate ophthalmic suture and an appropriate antibiotic and steroid regimen will be administered in the subconjunctival space, as follows:

1. Betamethasone (4mg)
2. Cefuroxime (125mg)

If betamethasone or cefuroxime are not available, then alternative subconjunctival steroids and antibiotics may be substituted, after contacting the Chief Investigator for prior approval.

8.2.12 Post-Op Regimen

Immediately after the procedure, a patch and shield will be applied to the treated eye, which will be left in place per instructions from the investigator.

The following post-op regimen will be prescribed:

- Maxitrol q.i.d. for 7 days followed by a tapering regimen for the next 21 days
- Atropine 1% b.i.d. for the next 14 days

The following alternative medications can be substituted for Maxitrol and Atropine, but all subjects must receive a topical steroid, antibiotic, and mydriatic:

- Tobradex q.i.d for 7 days followed by a tapering regimen for the next 21 days
- Betnesol-N q.i.d for 7 days followed by a tapering regimen for the next 21 days
- Maxidex q.i.d for 7 days followed by a tapering regimen for the next 21 days
- Prednisolone 1.0% q.i.d for 7 days followed by a tapering regimen for the next 21 days
- Cyclopentolate 1% t.i.d for the next 14 days
- Chloramphenicol 0.5% q.i.d for next 14 days

Subjects will be instructed that in the event of pain or sudden drop in vision, they should call the emergency number provided by the investigator.

9 EVALUATION OF EFFICACY

Efficacy assessments will include number of re-treatment injections, BCVA, fluorescein angiograms, optical coherence tomography, and colour fundus photographs. Whenever possible, the same person should perform the evaluations specified by the protocol at each study visit.

9.1 ETDRS Best-Corrected Visual Acuity (BCVA)

Manifest refraction and BCVA measurement must be performed according to the standard procedure originally developed for ETDRS and adapted for the Age Related Eye Disease Study (AREDS) protocol. For subjects in Arm A (VIDION[®]) either an ETDRS visual acuity or a Snellen visual acuity are adequate for visits on Day 1 and Week 1. The visual acuity assessor at these two time points need not be certified for visual acuity assessments, *but they must not*

subsequently undertake visual acuity assessment on the same patient, so that subsequent visual acuity assessment remains masked to the treatment arm. The treating ophthalmologist must not test visual acuity at any time point except Day 1 and Week 1. The method for assessing BCVA is specified in Appendix 3.

9.2 Fundus Fluorescein Angiography (FFA) and Colour Fundus Photography.

Fluorescein angiography will be performed on all study subjects using digital fluorescein photographic equipment systems certified by a central reading centre. All fluorescein images, from screening through to follow-up, will be read by masked evaluators at the central reading centre for an independent assessment. The technician who undertakes fluorescein angiography will remain masked to the treatment allocation.

The reading centre retained for this study is the Central Angiographic Resource Facility (CARF). CARF has a network of Reading Centres located in the Queen's University Belfast, Moorfield's Eye Hospital, London, and in St Paul's Eye Unit in the Royal Liverpool University Hospital. The contact details are:

Central Angiographic Resource Facility
Ophthalmic Research Centre
Queen's University of Belfast
Belfast BT12 6BA
Tel: 028 9063 2516 and 028 9063 2621
Fax: 028 9063 2666
Email: carf@qub.ac.uk
Web http://www.qub.ac.uk/carf/ReadingCentres/RC_home.html

CARF will certify the photographic technician prior to his or her involvement in the study, and will provide training if required. Colour fundus photographs will be acquired using the protocol specified by CARF. In brief, centres will capture a red-free and colour stereo images of two fields, and a calibration image showing the disc and macula. The FFA will capture early, mid and late images.

Protocol mandated FFAs and colour fundus photographs should be sent to CARF no more than 14 days after their acquisition.

9.3 Optical Coherence Tomography (OCT)

OCT will be utilised to assess subretinal fluid, intraretinal thickening, and neovascular lesions at each visit. At each of the monthly visits the Investigator will review the subject's OCT. At set visits (Baseline and Month 12 and 24) the OCT will also be sent to the CARF reading centre for masked assessment. The details of the reading centre are given in the section above. The OCT machine and technician will be certified by CARF prior to study commencement, and OCTs will be acquired using the protocol specified by the reading centre.

Monthly OCT images that are not sent for central reading should be captured using the same approved device, technician, and technique of image acquisition. The OCT software will provide an objective central retinal thickness reading in the central 1 mm subfield. This reading is used, alongside other criteria (Section 7.7), to determine if retreatment is required. This automated reading should be checked for error as it is possible that the OCT software fails to correctly identify the inner and outer neural retina limits correctly. To check for error it is best to review a higher magnification radial line scan. If there is error then a manual reading of OCT central neural retina thickness should be used for retreatment decisions, and it should be recorded in the CRF that a manual reading was taken. The thickness measurement should be centred on the fovea. The thickness measurement should extend from the inner limiting membrane up to, but not including, the retinal pigment epithelium.

The technician who undertakes OCTs should remain masked to the treatment allocation.

OCTs that require central reading should be sent to CARF no more than 14 days after their acquisition.

10 ADVERSE EVENT REPORTING AND DOCUMENTATION

10.1 Adverse Events Reporting

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

- The summary of product characteristics (SPC) for that product (for products with a marketing authorisation)
- The Investigator's Brochure (IB) relating to the trial in question (for any other investigational product)

Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

- Results in death;
- Is life-threatening;
- Required hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect.

In the unlikely event of the subject become pregnant, this should be recorded as an SAE,

Reporting of SAEs, SARs and SUSARs as multi-centre study

The Principal Investigator, with responsibility at each research site must report all SAEs, SARs and SUSARS (Suspected Unexpected Serious Adverse Reactions) immediately as the trial personnel become aware of the event to the Chief Investigator, or the organising research team on the form specified. The Principal Investigator or his/her research team must also follow all SAEs, SARs and SUSARs through to outcome, and report to Chief Investigator, or the organising research team on the form specified.

Contact details of Chief Investigator:

Mr Tim Jackson
Kings College Hospital,
Denmark Hill,
London SE5 9RS
Tel: 020 3299 1297
Fax: 020 3299 1721
Email: ritidesai@nhs.net

Chief Investigator will report all SAEs, SARs and SUSARs from all the research sites to Joint Clinical Trials Office (JCTO) immediately.

Contact details for submission of SAEs, SARs and SUSARs at JCTO:

Fax: 020 7188 8330
Email: Jackie.pullen@kcl.ac.uk

Reporting Responsibilities

King's College Hospital NHS Foundation Trust, as sponsor, have delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004) to the JCTO.

All SAEs, SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately by the Chief Investigator to the JCTO in accordance with the current Pharmacovigilance Policy.

Death as a result of disease progression and other events that are primary or secondary outcome measures are not considered to be SAEs and should be reported in the normal way, on the appropriate CRF.

The JCTO will report SUSARs and other SARs to the regulatory authorities (MHRA or competent authorities of other EEA (European Economic Area) states in which the trial is taking place).

The Chief Investigator will report to the relevant ethics committees. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.

The Chief Investigator will provide an annual report of all SARs (expected and unexpected), and SAEs which will be distributed to the Sponsor (JCTO), MHRA and the REC.

In considering this definition, the investigator should treat as “serious” any adverse effect that is life/sight-threatening (even if the threat to life/sight is temporary), results in permanent impairment of a body function or permanent damage to a body structure, or necessitates a medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

A list of anticipated adverse events and the appropriate terms to use are provided in the source documents.

10.2 Adverse Event Documentation

All Adverse Events must be recorded in the subject’s source documents and transferred to the appropriate CRF. As defined in the sections that follow, it should be recorded whether a given Adverse Event is:

-
- associated with or caused by the device
 - expected or unexpected
 - mild, moderate or severe intensity.

10.3 Adverse Event Criteria

10.3.1 Intensity

The following categories of the intensity of an adverse event are to be used:

Mild: Awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no sequelae;

Moderate: Interferes with the subject's usual activity, but the subject is still able to function;

Severe: Events that interrupt a subject's usual daily activity and generally require a systemic drug therapy or other treatment.

10.3.2 Relatedness

The Principal Investigator (PI) will evaluate if the AE or SAE is related to Lucentis[®], the VIDION[®] System, the vitrectomy procedure, or the injection procedure.

Relatedness is defined in the following manner:

Not related Evidence indicates no plausible direct relationship to the study device/medication

Unlikely Suggests other conditions are reasonably likely to account for the event including concurrent illness, progression or expression of the disease state, or reaction to concurrent medication

Possibly Suggests that the association of the event with the study device/medication is unknown; however, the adverse event is not reasonably supported by other conditions

Likely Suggests that a reasonable temporal sequence of the event with the study device/medication administration exists and, based upon the investigator's clinical experience, the association of the event with study device/medication seems likely

Definitely Suggests that the event and the study device/ medication has a reasonably likely association based upon the investigator's clinical experience and the event is unlikely to be related to other conditions.

10.3.3 Outcome

The clinical outcome of the AE or SAE will be characterised as follows:

- 1. Subject Recovered**
- 2. Resolved with sequelae**
- 3. Event Continuing**
- 4. Subject Died**

10.3.4 Treatment or Action Taken

Treatment or Action Taken will be defined in the following manner:

- 1. None**
- 2. Surgical Intervention**
- 3. Medical Intervention**
- 4. Other**

11 STATISTICAL ANALYSIS

11.1 Study Design and Randomisation

This is a prospective, randomised, controlled, multicentre study designed to assess the safety and efficacy of the VIDION[®] Ophthalmic System for the treatment of subfoveal choroidal neovascularisation associated with wet AMD.

Subject randomisation will be performed using a 2:1 allocation ratio with two VIDION[®] System subjects randomised for each control (Lucentis[®] monotherapy) subject. The randomisation code will be generated using stratified randomisation based on the lens status (phakic or pseudophakic) and lesion type (classic, minimally classic, or occult). Randomisation will be performed using the online facility incorporated into the system used for the electronic CRF. The electronic CRF system will require the Investigator to input inclusion and exclusion criteria data. This will be used to determine if the patient is eligible for inclusion in the study. If eligible, randomisation will occur automatically.

The effect of treatment on the principal endpoints will be assessed using Analysis of Covariance (ANCOVA) with the primary analysis including baseline severity and the stratification factors lens status and lesion type. Further sensitivity analyses will investigate the effects of confounders and will allow for interactions to be taken into account. These analyses will assume that both endpoints follow Normal distributions. Where this assumption is not tenable alternative analyses will be performed. For the secondary endpoints, logistic regressions will be used to assess the treatment effect on the percentage of subjects losing or gaining a given level of ETDRS letters and linear regressions for the change in total lesion size and CNV by fluorescein angiography.

11.2 Sample size calculation

The MERLOT study will compare the VIDION[®] System to the current NICE approved regimen of Lucentis[®] monotherapy. The co-primary outcome measures are mean change in ETDRS visual acuity and mean number of Lucentis[®] injections required per patient, per year.

The aim is to show that the VIDION[®] system reduces the number of Lucentis[®] injections but does not result in an inferior visual outcome.

Several criteria are used to establish the margin of non-inferiority. These include:

1. The effect size of the control to be used in the non-inferiority study relative to no treatment. The margin must be small enough so that a demonstration of non-inferiority of the experimental treatment to the control implies that the experimental treatment is superior to no treatment.
2. The proportion of the effect Size that must be maintained in the non-inferiority study. The margin is often chosen to be 50% of the effect size.
3. How do other treatments compare to the non-inferiority region established by the Margin?
4. Will subjects still experience a benefit from the treatment if the results are close to the lower edge of the non-inferiority region?

Assumptions are based on Year 1 outcome data from the PrONTO study³⁶ (Prospective Optical coherence tomography imaging of patients with Neovascular AMD Treated with intra-Ocular ranibizumab) of 'as required' Lucentis[®] therapy, as patients entering the present MERLOT study will do so having already commenced treatment. Therefore the final outcome visual acuity in the PrONTO study is assumed to be the same as the presenting visual acuity in the MERLOT study. Presenting visual acuity is therefore assumed to be 65.5 ETDRS letters (standard deviation 14.6 in both groups). With an allocation ratio of 2:1 (device:control), alpha 0.05, power 90%, and a non-inferiority margin of 5 ETDRS letters (>1 line loss of visual acuity) group sample sizes were calculated to be 220 (device) and 110 (control). An additional 10% were added to give a final target of 363 subjects.

The PrONTO study of 'as required' Lucentis[®] treatment found that patients required a mean of 5.6 injections over the first year of treatment and NICE estimates eight injections in the first year (of which three are induction treatment), and six in year 2. Based on the inclusion criteria, the present study assumes a higher mean number of injections in the study subjects of 8.0 per year. With group sample sizes of 220 (VIDION[®]) and 110 (Lucentis[®]) the study will have greater than 90% power to detect a difference of 2.0 injections (8 in the control vs 6 in the device group), based on the estimated group standard deviations of 3.0 injections (device) and 4.0 injections (control) and a significance level of 5%.

11.3 Study Endpoints

11.3.1 Co-primary Endpoint- Treatment Success

Efficacy of the VIDION[®] System will be assessed with respect to its ability to prevent loss of visual acuity and its ability to reduce patients' reliance on 'as required' Lucentis[®] injections.

Visual acuity will be assessed by measuring by the mean number of letters read on an ETDRS Chart. Consequently, the change-from-baseline in the number letters read will be assessed for each subject enrolled in the study:

Change-from-baseline ETDRS value is defined as the difference between the follow-up and baseline ETDRS values. A positive change indicates a gain in vision from baseline, whereas a negative result indicates a loss in vision. The baseline value is obtained from the assessment performed at the visit when the subject is treated with the VIDION[®] Ophthalmic System or Lucentis[®].

To summarise, the main outcomes are:

1. Mean Change in Vision (non-inferiority): The outcome is mean change of ETDRS visual acuity at 12 months compared to baseline.
2. Reduction in 'as required' Lucentis[®] injections: The outcome is mean number of 'as required' Lucentis[®] injections required, per patient, per year.

11.3.2 Secondary Endpoints

Secondary efficacy parameters will be measured and compared between the two treatment groups at Month 12:

- Percentage of subjects losing < 15 ETDRS letters
- Percentage of subjects gaining ≥ 0 ETDRS letters
- Percentage of subjects gaining ≥ 15 ETDRS letters
- Change in total lesion size by fluorescein angiography
- Change in total CNV size by fluorescein angiography
- Foveal thickness measured using OCT.

11.4 Safety

All AEs will be followed through to resolution or 30 days after the subject terminates from the study, whichever occurs first. The three year duration of the study has been selected to ensure a protracted assessment of safety.

11.5 Interim Analyses

Interim analyses will be conducted using an O'Brien-Fleming stopping rule for each of the primary endpoints. The frequency of these interim analyses will be agreed with the data monitoring committee (DMC) and the details will be pre-specified in the DMC charter.

Additionally the assumptions underlying the sample size calculations will be assessed and sample size re-estimation using conditional power calculations will be undertaken.

12 QUALITY ASSURANCE, DATA HANDLING AND RECORD RETENTION

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained by the Joint Clinical Trials Office (JCTO) Quality Team.

The Investigator will act as custodian for the trial data at each site. The following guidelines will be strictly adhered to:

- Patient data will be anonymised
- All anonymised data will be stored on a password protected computer
- All trial data will be stored and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Joint Clinical Trials Office Archiving SOP.

The local Principal Investigator shall maintain all study records until notified by the Chief Investigator that retention is no longer required. If the investigator moves from the site at which he/she conducted the study and/or maintained the study records, the investigator shall notify the Chief Investigator in writing whether the records will remain at the site at which the

study was conducted or be moved to another location, and if another location, where and under whose custody. The investigator shall notify the Sponsor as soon as possible in the event of destruction or loss of any study records.

13 DATA MONITORING COMMITTEE AND TRIAL STEERING COMMITTEE

13.1 Data monitoring committee (DMC)

The DMC will have access to unblinded data to monitor safety and will make recommendations to the Trial Steering Committee. The DMC will adhere to the terms of the DMC charter shown in Appendix 4. The members of the DMC are shown at the start of the protocol.

13.2 Trial Steering Committee

The Trial Steering Committee will supervise the trial and ensure that it is conducted in accordance with the principles of Good Clinical Practice, and that it complies with all applicable regulations. The Trial Steering Committee will approve any protocol amendments. The Committee will oversee trial quality, including data handling, protocol non-compliance and deviations. They will review the recommendations of the DMC and amend the protocol as necessary. The Trial Steering Committee will meet at least every 6 months in Year 1, and at least annually thereafter, with additional meetings as necessary. They will maintain minutes of meeting and provide any reports requested by the Research Ethics Committee and MHRA.

14 INFORMED CONSENT

The investigator is responsible for obtaining the legally effective informed consent of the subject or the subject's legally authorised representative. In carrying out this responsibility, the investigator (and other involved team members) should recognise that informed consent is not just a signature on an informed consent form, but a process during which the subject and those with whom the subjects wishes to consult (such as family members, friends, and personal physicians) are provided with sufficient information about the study and under circumstances

that allow the subject to consider whether or not to participate and to minimise the possibility of undue influence or coercion.

Once the EC has approved the Patients Information Sheet and Informed Consent Form, the form should be used as the basis of the information presented to the subject during the informed consent process. The form should be provided to the subject early in the process, so that he/she has ample time to read it and discuss it with others if he or she wishes to do so.

Each of the following key elements must be discussed with the subject:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that regulatory authorities and external monitors may inspect the records.
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

-
- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or foetus, if the subject is or may become pregnant) which are currently unforeseeable.
 - Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
 - Any additional costs to the subject that may result from participation in the research.
 - The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

Once the informed consent process is complete and the subject has reached a decision as to whether to participate, the investigator should record the decision in the case history form. If the subject decides to participate, he or she should be asked to sign the Informed Consent Form. A copy of the signed form should be given to the subject, and the signed form should be included with the subject's study records.

If there is any new information which may affect a subject's willingness to continue participation in the trial, he or she will be re-consented with an amended or supplementary Patient Information Sheet and Consent Form.

15 DATA MANAGEMENT

All study data will be entered into the electronic CRFs. All requested information must be entered on the CRF. If an item is not available or not applicable this fact should be indicated. Data management must comply with the Data Protection Act 1998. The electronic CRF will allow interim safely analysis by the data monitoring committee and validation of data entry. The data management team and study monitors may raise queries using the electronic system, and the study site Investigator must provide a response in a timely manner.

Interim analyses will be conducted at six-monthly intervals to coincide with the Data Monitoring Committee meetings. The significance level and effect estimates for these analyses will be adjusted for the sequential nature of the inspections according to double triangular stopping boundaries. Classification of missing data will be performed by modelling the likelihood of missingness using logistic regressions and multiple data imputation will be used, as necessary, to verify the validity of the models.

16 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

The investigator(s) shall permit trial-related monitoring, audits, REC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (i.e. patients' case sheets, blood test reports, X-ray reports, histology reports etc). Where necessary, inspection may also take place at site's facilities.

17 RECORDKEEPING

The investigator must maintain the following accurate, current, and complete records relating to his/her participation in the study:

- All correspondence with another investigator, an EC, the Sponsor, a monitor, including required reports
- Device Accountability Records including the type and quantity of the device received, the dates of receipt, the serial number for each device, and the name of each person who received and/or used each device
- Records of each subject's source documents and exposure to the device, including signed and dated consent forms and medical records, progress notes, hospital or clinical charts and nurses' notes
- All relevant observations, including records concerning adverse device effects, information and data on the condition of the subject upon entering and during the course of the study, including information about relevant previous medical history and the results of all diagnostic tests
- The protocol, with documents showing the dates of and reasons for each deviation from the protocol
- CRFs
- Fundus Fluorescein Angiography and Optical Coherence Tomography Images

All study records should be maintained in a locked, limited-access area.

18 PUBLICATION POLICY AND FINANCIAL ASPECTS

It is intended that the results from this study be published in peer reviewed medical journals. Key outcome data will be reported following completion of the Month 12 dataset. A supplementary report will detail outcome data at Year 2. It is intended that these two publications will be submitted by the MERLOT study group. The MERLOT study group will comprise researchers who have made a significant contribution to study design, recruitment, statistical analysis, or manuscript preparation. Researchers who have contributed substantially more than most members of the MERLOT study group may be invited by the Chief Investigator to submit these or other manuscripts on behalf of the MERLOT study group, in which their name appears on the title page as an author or co-author. The authorship list and order for these and any other publications will be determined by the Chief Investigator.

Researchers involved in this study will submit all data for pooled analysis by the Chief Investigator. Researchers will not present, publish or disseminate any study data, including case reports and case series, without the prior permission of the Chief Investigator.

This investigator initiated trial is sponsored King's College Hospital NHS Foundation Trust, who own any intellectual property arising from the trial. Clinical Negligence Scheme for Trusts (CNST) provides indemnity that covers clinical negligence and harm caused.

The device manufacturer (NeoVista Inc) will provide an unrestricted grant to King's College Hospital NHS Foundation Trust to support research costs. The device manufacturer provided material that was used in the CABERNET study protocol that was adapted for use in the MERLOT protocol. NeoVista may provide source documents that were based on templates developed for the CABERNET study, and additional research or financial support at the request of the Sponsor.

King's College Hospital NHS Foundation Trust will contract with participating sites to undertake the research and will pay these sites to recruit patients. Participating sites will contract with the device manufacturer to purchase the VIDION[®] device and lease the radiation source. Treatment costs will be funded by the relevant health commissioning agency, which will usually be the local Primary Care Trust. Researchers must ensure that the relevant healthcare commissioning agency has agreed to fund the treatment costs prior to study commencement.

19 INVESTIGATOR REPORTS

19.1 Adverse Event Report

Adverse event reporting will be performed according to the procedures described in Section 10.1.

20 REFERENCES

1. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene and zinc for age-related macular degeneration and vision loss. *Arch Ophthalmol* 2001; 119:1417-1436.
2. Ferris FL, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol* 1984; 102:1640-1642.
3. Macular Photocoagulation Study Group. Persistent and recurrent neovascularisation after krypton laser photocoagulation for neovascular lesions of age-related macular degeneration. *Arch Ophthalmol* 1990; 108:825-831.
4. Young RW. Pathophysiology of age-related macular degeneration. *Surv Ophthalmol* 1987:291-306.
5. Eagle RC. Mechanisms of maculopathy. *Ophthalmology* 1984; 91:613-625.
6. Friedman E ,Ivry M, Ebert E, Glynn R, Gragoudas E, Seddon J. Increased scleral rigidity and age-related macular degeneration. *Ophthalmology* 1989; 96:104-108.
7. Friedman E. A hemodynamic model of the pathogenesis of age-related macular degeneration [editorial]. *Am J Ophthalmol* 1997; 124(5): 677-682.
8. Lopez PF, Sippy BD, Lambert HM, Thach AB, Hinton DR. Transdifferentiated retinal pigment epithelial cells are immunoreactive for vascular endothelial growth factor in surgically excised age- related macular degeneration-related choroidal neovascular membranes. *Invest Ophthalmol Vis Sci* 1996; 37:855-868.
9. Ohno Matsui K, Morita I, Tombran-Tink J, Mrazek D, Onodera M, Uetama T, Hayano M, Murota S, Mochizuki M. Novel mechanism for age-related macular degeneration: an equilibrium shift between the angiogenesis factors VEGF and PEDF. *J Cell Physiol* 2001;189:323-333.
10. Campochiaro PA, Soloway P, Ryan SJ, Miller JW. The pathogenesis of choroidal neovascularization in patients with age-related macular degeneration. *Mol Vis* 1999; 35:34.
11. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med*. 2004;351:2805-2816.
12. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1419-1431.
13. Brown DM, Kaiser PK, Michels M, et al, for the Anchor Study Group. Comparison of ranibizumab and verteporfin photodynamic therapy for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1432-1444

-
14. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study Year 1. *Am J Ophthalmol* 145. 239-248.2008.
 15. Lucentis® Prescribing Information. Available at: <http://www.gene.com/gene/products/information/pdf/lucentis-prescribing.pdf>
 16. Krishnan L, Krishnan EC, Jewell WR. Immediate effect of irradiation on microvasculature. *Int J Radiat Oncol Biol Phys* 1988; 15:1147-1450.
 17. Chakravarthy U, Gardiner TA, Archer DB, Maguire JF. A light microscopic and autoradiographic study of non-irradiated and irradiated ocular wounds. *Curr Eye Res* 1989; 8:337-348.
 18. Mooteri SN, Podolski JL, Drab EA, Saclarides TJ, Onoda JM, Kantak SS, Rubin DB. WR-1065 and radioprotection of vascular endothelial cells, II: morphology. *Radiat Res* 1996; 145:217-224.
 19. Rosander K, Zackrisson B. DNA damage in human endothelial cells after irradiation in anoxia. *Acta Oncol* 1995; 34:111-116.
 20. Rubin DB, Drab EA, Kang HJ, Baumann FE, Blazek ER. WR-1065 and radioprotection of vascular endothelial cells, I: cell proliferation, DNA synthesis and damage. *Radiat Res* 1996; 145:210-216.
 21. Verheij M, Koomen GCM, van Mourik JA, Dewitt L. Radiation reduces the cyclooxygenase activity in cultured human endothelial cells at low doses. *Prostaglandins*. 1994; 48:351-366.
 22. Hosoi Y, Yamamoto M, Ono T, Sakamoto K. Prostacyclin production in cultured endothelial cells is highly sensitive to low doses of ionizing radiation. *Int J Radiat Biol* 1993; 63:631-638.
 23. Hallahan D, Clark ET, Kuchibhotla J, Gewertz BL, Collins T. E-selectin gene induction by ionizing radiation is independent of cytokine induction. *Biochem Biophys Res Commun* 1995; 217:784-795.
 24. Eissner G, Kohluhuber F, Grell M, Ueffing M, Scheurich P, Hieke A, Multhoff G, Bornkamm GW, Holler E. Critical involvement of transmembrane tumor necrosis factor- α endothelial programmed cell death mediated by ionizing radiation and bacterial endotoxin. *Blood* 1995; 86:4184-4193.
 25. Archer DB, Amoaku WM, Gardiner TA. Radiation retinopathy- clinical, histopathological, ultrastructural and experimental correlations. *Eye* 1991; 5:239-251.
 26. Maguire AM, Schachat AP. Radiation retinopathy. In: *Retina*. St. Louis: Mosby- 1994.
 27. Parsons JT, Fitzgerald CR, Hood CI, Ellingwood KE, Bova FJ, Million RR. The effects of irradiation on the eye and optic nerve. *Int J Radiat Oncol Biol Phys* 1983;9:609-622.
 28. Bergink GJ, Deutman AF, van den Broek JF, van Daal WA, van der Maazen RW, . A randomized controlled clinical trial on the efficacy of radiation therapy in the control of subfoveal choroidal neovascularization in age-related macular degeneration: radiation versus observation. *Graefes Arch Clin.Exp.Ophthalmol* 1998; 236:321-325.
 29. Chakravarthy U, Houston RF, Archer DB. Treatment of age-related subfoveal neovascular membranes by teletherapy: a pilot study. *Br J Ophthalmol*. 1993;77:265-273.
 30. Char DH, Irvine IA, Posner MD, Quivey J, Phillips TL, Kroll S. Randomized trial of radiation for age-related macular degeneration. *Am.J Ophthalmol* 1999;127:574-578.
 31. Jaakkola A, Heikkonen J, Tommila P, Laatikainen L, Immonen I. Strontium Plaque Brachytherapy for Exudative Age-Related Macular Degeneration: Three-Year Results of a Randomized Study. *Ophthalmology* 112[4], 2005; 567-573.28

-
32. Jaakkola A, Heikkonen J, Tommila P, Laatikainen L, Immomen I. Strontium plaque irradiation of subfoveal neovascular membranes in age-related macular degeneration. *Graefes Arch.Clin.Exp.Ophthalmol.* 1998; 236:24-30.
 33. Finger PT, Berson A, Ng T, Szechter A. Ophthalmic plaque radiotherapy for age-related macular degeneration associated with subretinal neovascularization. *Am J Ophthalmol* 1999; 127:170-177.
 34. Avila MP, Farah ME, Duprat JP *et al.* Twelve month short-term safety and visual acuity results from a multicentre prospective study of epiretinal strontium-90 brachytherapy with bevacizumab for the treatment of subfoveal choroidal neovascularisation secondary to age-related macular degeneration *Br J Ophthalmol* 2009;93:305–9.
 35. Macugen[®] Prescribing Information. Available at: http://www.macugen.com/macugen_PI.pdf
 36. Fung AE, Lalwani GA, Rosenfeld PJ, Dubovy SR, Michels S, Feuer WJ, Puliafito CA, Davis JL, Flynn HW Jr, Esquiabro M. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Am J Ophthalmol.* 2007 Apr;143(4):566-83
 37. Sagerman RH, Chung CT, Alberti WE: Radiosensitivity of ocular and orbital structures. In: WE Alberti, RH Sagerman, Eds. *Radiotherapy of Intraocular and Orbital Tumors*, 2nd Revised Edition. Berlin-Verlag, 2003.
 38. Espallargues M. Czoski-Murray CJ. Bansback NJ. Carlton J. Lewis GM. Hughes LA. Brand CS. Brazier JE. The impact of age-related macular degeneration on health status utility values. *Investigative Ophthalmology & Visual Science.* 46(11):4016-23, 2005 Nov.

Statistical Analysis Plan

MERLOT Trial

Macular EpiRetinal Brachytherapy versus Lucentis® Only Treatment

A study of epimacular brachytherapy for AMD

EudraCT Number: 2009-012509-20

Lead Statistician: Professor Toby Prevost, Kings College London

Trial Statistician: Dr Abdel Douiri, King's College London

Chief Investigator: Mr Tim Jackson, King's College Hospital

Chair of Trial Steering Committee: Mr Richard Wormald

Chair of Data Monitoring Committee: Professor Desmond Archer

Study Sponsor: King's College Hospital

Funded by NeoVista

Version 2.1

28th November 2012

CONTENTS

- 1.0 Introduction**
 - 1.1 Derivation of the statistical analysis plan
 - 1.2 Purpose and scope of the statistical analysis plan

- 2.0 Overview from NICE report**
 - 2.1 Description of the condition and treatment
 - 2.2 Use of brachytherapy and potential adverse effects

- 3.0 Populations and Study Sample**
 - 3.1 Target Population
 - 3.2 Trial Population
 - 3.3 Trial Sample
 - 3.4 Inclusion and Exclusion criteria
 - 3.5 Safety analysis population

- 4.0 Objective, principal research question and associated hypotheses**
 - 4.1 Trial objectives
 - 4.2 Principal Research Question
 - 4.3 Hypotheses
 - 4.4 Possible study outcomes by the combination of the co-primary outcomes
 - 4.5 Adjustment to significance level to account for two co-primary outcomes

- 5.0 Trial design**
 - 5.1 Treatment arms
 - 5.2 Re-Treatment Criteria

- 6.0 Trial measures**
 - 6.1 Superiority co-primary outcome
 - 6.2 Non-inferiority co-primary outcome
 - 6.3 Secondary efficacy outcomes measures
 - 6.4 Safety outcomes
 - 6.5 Timing of measures
 - 6.6 Final assessment
 - 6.7 Participant duration of study

- 7.0 Sample Size**
 - 7.1 Determination of the visual acuity margin
 - 7.2 Determination of the visual acuity outcome variability.
 - 7.3 Clustering of outcomes from eyes within subjects
 - 7.4 Determination of the sample size based on the visual acuity outcome
 - 7.5 Power to detect effects on number of injections.
 - 7.6 Detectable effects sizes for secondary outcomes

- 8.0 Randomisation, Subgroups and Confounders**
 - 8.1 Arms
 - 8.2 Method of allocation
 - 8.3 Relative timing of randomisation
 - 8.4 Subgroup variables

- 9.0 Distributional considerations**
 - 9.1 Use of data transformation
 - 9.2 Defining Outliers
 - 9.3 Handling outliers
 - 9.4 Model assumptions

- 10.0 Descriptive analysis**
 - 10.1 Flow diagram
 - 10.2 Baseline comparability of randomised groups
 - 10.3 Comparison of rates

- 11.0 Analysis covariates**
 - 11.1 Stratifiers
 - 11.2 Baseline

- 12.0 Analysis of co-primary outcomes**
 - 12.1 Injections
 - 12.2 Visual Acuity
 - 12.3 Sensitivity analysis for primary outcomes
 - 12.4 Conditions for testing for superiority

- 13.0 Analysis of secondary outcomes**
 - 13.1 Continuous outcomes
 - 13.2 Binary outcomes
 - 13.3 Baseline Subgroups
 - 13.4 Presentation

- 14.0 Cataracts**
 - 14.1 Importance
 - 14.2 Analyses

- 15.0 Handling multiple comparisons**

- 16.0 Software**

- 17.0 References**

- 18.0 DMC monitoring**

- 19.0 Acknowledgments**

- 20.0 Amendments to Versions**

- 21.0 Appendix 1 – Record post blind-break**
 - 21.1 Record of data decisions
 - 21.2 Record of analysis decisions

ABBREVIATIONS

AMD	Age-Related Macular Degeneration
ANCOVA	Analysis of Covariance
Anti-VEGF	Antivascular endothelial growth factor agents
BCVA	Best Corrected Visual Acuity
CNV	Choroidal Neovascularisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CRF	Case Report Form
DMC	Data Monitoring Committee
ETDRS	Early Treatment Diabetic Retinopathy Study
ICH	International Conference on Harmonization
IOP	Intraocular pressure
ITT	Intention To Treat
LOCF	Last Observation Carried Forward
NICE	National Institute for Health and Clinical Excellence
OCT	Optical Coherence Tomography
RAP	Retinal Angiomatous Proliferation
TSC	Trial Steering Committee

SYNONYMS

Avastin®	Bevacizumab
Lucentis®	Ranibizumab

1.0 Introduction

1.1 Derivation of the statistical analysis plan

Version 1.1 (dated 21st October 2012) of the Statistical Analysis Plan (the “Plan”) was derived from the Research Protocol (Version 4) by the lead statistician (Toby Prevost) who is masked to outcome data.

Relevant NICE reports (2011, 2012) and the methods used in recently completed randomised controlled trials (ABC, CABERNET, CATT) have been taken into account.

The Plan was then be amended to Version 2.1 (the current version) after a meeting with the Chief Investigator (Tim Jackson) and DMC statistician (Catey Bunce). This will be sent to the full DMC and the Trial Steering Committee resulting in amendment and approval as Version 3. It will then be lodged with a statistician independent of the study.

Later amendment to the Plan will only be considered prior to unmasking of the trial outcome data by study arm. Such amendments would be approved through a repeat of this process just outlined.

The Trial Statistician (Abdel Douiri), who undertakes the DMC reports, will undertake the final trial analysis according to the approved Plan.

The MERLOT Research Protocol necessarily contains extensive information, and so the Statistical Analysis Plan draws in those parts of the protocol necessary to provide the clinical context for laying out, and explaining the basis of, the analysis strategy. It is intended for the Plan to stand alone, though the Research Protocol is available for further protocol detail.

The Plan is written by a statistician, and in a ‘non-medical’ language and style which should allow the trial analysis statistician to proceed with the statistical procedures within the trial analysis. Therefore the explanations will not necessarily always be phrased medically precisely, though aiming to be sufficiently accurate, clear and unambiguous for the required purpose.

1.2 Purpose and scope of the statistical analysis plan

The purpose of this Statistical Analysis Plan is to set out the study objectives and hypotheses, and the analytical approaches and procedures necessary to address these for the main trial paper and to provide guidance for further research reported in other papers, promoting consistent approaches and methods. These further papers are anticipated to include a paper reporting on 24-month follow-up, and a paper examining safety and efficacy at the 3-year point.

As there can typically be more than one analytical approach to address a hypothesis, there is the potential for different results to be produced from using alternative approaches, alternative methods, alternative outcome definitions and alternative data

that may be involved. These differences can be influential, for example when results are of borderline statistical significance.

Therefore, this Plan records those decisions that can be made about study hypotheses, outcome definitions and statistical procedures, along with their basis and the appropriateness of the assumptions required for their use, in advance of the main trial analysis, while there access to unmasked follow-up data and trial arm is prevented.

Changes within subsequent versions of the Plan prior to analysis will be dated, with the basis for the changes reasoned, and recorded within the plan.

Other analysis decisions may need to be made later, based on viewing the observed distribution of the follow-up data. Where possible these decisions will be made prior to access to trial arm, or where necessary from control arm data alone. Decisions will be supported by reasoning and justification, and these will appended to the Statistical Analysis Plan to provide a record of any post-analysis decisions and the basis.

It is not intended that the strategy set out in the plan should prohibit sensible practices. However, the principles established in the plan will be followed as closely as possible when analysing and reporting the trial.

The formation of the MERLOT Plan has drawn on statistical guidance from the ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials, the CONSORT statement for reporting trials (Schulz et al., 2010), and the Committee for Proprietary Medicinal Products report, methods from recent trials in the area, and NICE documents.

2.0 Overview from NICE report

NICE interventional procedures guidance (2012) provides the following summary:

2.1 Description of the condition and treatment

Age-related macular degeneration (AMD) affects the area of the back of the eye that is responsible for central vision (the macula). There are two types – ‘dry’ and ‘wet’. The wet form is caused by bleeding from the formation of new blood vessels. Loss of vision is then progressive and often rapid.

A current treatment is anti-VEGF injections (injections of antivascular endothelial growth factor agents), which work by blocking a substance that causes new blood vessels to grow in the eye. Radiotherapy has been used in people with wet age-related macular degeneration to treat the new blood vessels growing under the macula. A probe is carefully inserted into the eye through a small incision and radiation therapy is used to destroy the new blood vessels. The aim of this procedure is to slow down sight loss or stabilise the patient’s vision.

Epiretinal (epimacular) brachytherapy for wet AMD aims to slow down the growth of blood vessels that cause wet AMD by administering beta radiation therapy targeted at the abnormal, leaking vessels.

2.2 Use of brachytherapy and potential adverse effects

In the NICE report it is stated that the procedure should only currently be used in the context of research; that research studies should address whether epiretinal brachytherapy reduces the progression of wet AMD and whether it can reduce the number of injections (of anti-VEGF) required; and that long-term outcomes should be reported.

The specialist advisers to NICE listed the key efficacy outcomes to be the retention of visual acuity, the number of anti-VEGF injections required, and the time to recurrence of AMD.

NICE was presented with the report of a case series of 34 patients treated by epiretinal brachytherapy plus anti-VEGF injections. The report indicated that 25% (6/24), 50% (12/24) and 54% (7/13) of phakic eye patients developed cataracts at follow-up periods of 12, 24 and 36 months. Other potential adverse events include increased intraocular pressure, retinal tear, and non-proliferative radiation retinopathy.

3.0 Populations and Study Sample

3.1 Target Population

The *target population*, to which inferences from the end of the MERLOT trial are intended to generalise, is the population of patients with subfoveal Choroidal Neovascularisation (CNV) associated with wet Age-Related Macular Degeneration (AMD).

3.2 Trial Population

The *trial population*, from which the study sample is drawn, is further defined to be patients aged 50 or older at commencement of anti-VEGF (Vascular Endothelial Growth Factor) therapy, who are treated at one of the multiple study sites around the United Kingdom, and who have been previously treated with ranibizumab (also known as Lucentis®).

3.3 Trial Sample

The achieved *trial sample* comprises those patients who consent to participate and are actually randomised into the MERLOT trial. These patients are the study subjects.

This randomised trial sample is also the trial *Intention To Treat (ITT) population*. Subjects will be analysed according to the treatment group to which they are randomised.

The trial ITT population comprises all randomised participants, regardless of eligibility (inclusion/exclusion) error, post-randomisation withdrawal, and whether the correct study treatments were received, or other interventions received.

3.4 Inclusion and Exclusion criteria

Inclusion criteria are as follows. Subjects must have met the NICE treatment criteria for Lucentis® therapy, and received anti-VEGF induction treatment, defined as the first three months of anti-VEGF therapy. Following this induction period, subjects must have received at least 4 additional injections of Lucentis® in no more than 12 months preceding enrolment, or 2 additional injections of Lucentis® in no more than 6 months preceding enrolment, given on an as needed basis; (for subjects who have received both Avastin® and Lucentis® treatment)

All of the following circumstances must apply in the eye to be treated:

- the Best Corrected Visual Acuity (BCVA) is between 6/12 and 6/96, corresponding to 24 to 69 ETDRS (Early Treatment Diabetic Retinopathy Study) letters
- there is no permanent structural damage to the central fovea
- the lesion size is less than or equal to 12 disc areas in greatest linear dimension
- there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes)

Exclusion criteria are listed in the protocol. A selection of these follow:

2. Visual acuity worse than 6/96 (24 ETDRS letters) at the time of enrolment;
6. Subjects who have been previously diagnosed with Type 1 or Type 2 Diabetes Mellitus or retinal findings consistent with these.
7. Subjects with advanced glaucoma (greater than 0.8 cup:disk) or intraocular Pressure (IOP) \geq 30 mmHg in the study eye;
8. Previous glaucoma filtering surgery in the study eye;
9. Subjects with inadequate pupillary dilation or significant media opacities in the study eye, including cataract, which may interfere with visual acuity or the evaluation of the posterior segment;
13. Subjects who have undergone any intraocular surgery in the study eye within 12 weeks prior to the screening visit, with the exception of cataract surgery as discussed in the Exclusion Criteria #14
14. Previous cataract surgery within 2 months prior to enrolment into the study;
19. Subjects with any other condition, which in the judgment of the investigator would prevent the subject from completing the study (e.g. documented diagnosis of dementia or serious mental illness).

3.5 Safety analysis population

The safety analysis population is comprised of those randomised subjects who receive at least one treatment with brachytherapy and/or Lucentis.

4.0 Objective, principal research question and associated hypotheses

4.1 Trial objectives

The objective of the MERLOT Trial is to evaluate the safety and efficacy of focal delivery of radiation for the treatment of subfoveal choroidal neovascularisation (CNV) associated with established wet age-related macular degeneration (AMD) previously treated with anti-VEGF therapy.

4.2 Principal Research Question

The Principal Research Question in the trial is as follows: Can epimacular brachytherapy radiation reduce the frequency of Lucentis® re-treatment that patients require, whilst maintaining visual acuity.

4.3 Hypotheses

There are several types of hypotheses, and relevant ones are listed as follows.

The hypotheses need to deal with two elements of potential change. These are: the change in visual acuity; and the change in the number of Lucentis® injections required.

Hypotheses refer to the populations of relevant patients rather than study subjects.

The Working hypothesis: The so-called ‘working hypothesis’ is the hypothesis which motivates the trial, which the trial results may or may not support. It is that epimacular brachytherapy does (indeed) reduce the frequency of ranibizumab (Lucentis®) re-treatment that patients require, whilst maintaining visual acuity.

The Statistical Null Hypothesis: Epimacular brachytherapy EITHER does not change the frequency of Lucentis® re-treatment that patients require OR visual acuity is inferior (OR BOTH).

The Null Hypothesis will be rejected in favour of an alternative hypothesis, if there is evidence of change in Lucentis® frequency (*judged from the trial sample by two-sided 5% significance level for the test of zero difference in mean injections between arms*) AND visual acuity is non-inferior (*the two-sided 95% confidence interval does not undercut an accepted margin of non-inferiority, judged by one-sided 2.5% significance level against the margin*).

Statistical Alternative hypothesis: Epimacular brachytherapy is BOTH non-inferior in terms of visual acuity, AND there is a change in number of required Lucentis® injections.

4.4 Possible study outcomes by the combination of the co-primary outcomes

Null and Alternative hypotheses in relation to the co-primary outcomes

Visual acuity is:	Injection frequency	Null Hypothesis	Alternative Hypothesis
Non-inferior	Change	False	True
Non-inferior	Same	True	False
Inferior	Change	True	False
Inferior	Same	True	False

Possible Outcomes from analysis:

If there is a significant reduction in injections and non-inferior visual acuity, then the null hypothesis will be rejected in favour of brachytherapy being efficacious for injection reduction while maintaining visual acuity.

If there is a significant increase in injections and non-inferior visual acuity, then the null hypothesis will be rejected, with the conclusion that brachytherapy increases injections and maintains visual acuity.

If non-inferiority of brachytherapy in visual acuity is not shown, then the null hypothesis will not be rejected, regardless of any positive or negative effect on number of injections.

Visual acuity	Judged by	Injection frequency	Judged by	Null Hypothesis	Supports Brachytherapy
Non-inferior	95%CI > margin	Change	P<0.05	Reject	If injections reduced
Non-inferior	95%CI > margin	Same	p>0.05	Keep	No
Inferior	95%CI not > margin	Change	P<0.05	Keep	No
Inferior	95%CI not > margin	Same	p>0.05	Keep	No

A margin of 5 letters is used (see later).

4.5 Adjustment to significance level to account for two co-primary outcomes

There are two co-primary outcomes: visual acuity and number of re-treatment injections of Lucentis® per year.

Normally there would be an adjustment for use of two co-primary outcomes to prevent an accumulation of false positive rate (i.e. rate of Type 1 error) above 5%. This occurs when statistical significance for either one (or both) of the outcomes individually triggers a rejection of the null hypothesis, irrespective of the other result. False positives can arise from the analysis of each outcome, and accumulate to a rate above 5%.

However, there is no need to adjust the significance levels in the MERLOT trial. These levels are 5% two-sided for injection frequency, and a 95% confidence interval below the margin. The latter is equivalent to a 2.5% level from a one-sided test.

There is no need to adjust the significance levels because the rejection of the null hypothesis requires rejection of both elements of the null hypothesis (rather than a trigger from either one). Similarly, false positives from the null hypothesis can arise only from the tests for both outcomes (visual acuity, injections) being declared positive falsely.

5.0 Trial design

5.1 Treatment arms

The trial is randomised, with two arms, and with unequal allocation of participants in the 2:1 ratio of **treatment** to **control**.

The arms are labelled for brevity as follows:

Arm A: Treatment: A single surgical procedure with epimacular brachytherapy using the VIDION® System, with Lucentis® (0.5 mg) administered on a monthly basis as required, using the re-treatment criteria below. This involves directional delivery of radiation to target tissues, required within 21 days of the start of screening.

Arm B: Control: Lucentis® (0.5 mg) administered on a monthly basis as required, using the re-treatment criteria below.

The arms are also referred to in this plan as A: brachytherapy, B: Lucentis® monotherapy, control, comparison.

5.2 Re-Treatment Criteria

Lucentis® should be administered if any of the following four conditions are met:

1. The subject has lost more than five ETDRS letters of visual acuity from baseline, and this is attributable to active wet AMD;
2. An increase of more than 50 microns in central retinal thickness from the lowest central retinal thickness measurement since screening secondary to new or increased subretinal, intraretinal, or sub-RPE fluid, as confirmed by OCT;
3. Presence of new, or an increase from the last visit in subretinal or intraretinal blood;
4. New neovascularisation as confirmed by fluorescein angiography

Lucentis® should be administered at Baseline for subjects in both arms if the above retreatment criteria apply. To determine if there is new disease activity or loss of visual acuity, Baseline and Screening observations should be compared to recent clinical observations.

Baseline treatment with Lucentis® in Arm A can be given concomitantly at the end of surgery, or given up to 21 days from the Screening Visit. At subsequent visits the observations used for retreatment decisions should be compared to other observations made during the subject's participation in the trial. Further details and clarification are provided in the protocol.

If the treating ophthalmologist decides that Lucentis® re-treatment would be beneficial for persisting subretinal, intraretinal, or sub-RPE fluid confirmed on OCT, but the re-treatment criteria are not fulfilled, then he or she may administer Lucentis®, but this should be recorded as a deviation.

If the eye does not show a decrease in fluid after three consecutive monthly injections, the treating ophthalmologist may choose to suspend treatment. Treatment may be re-initiated if the subretinal, intraretinal, or sub-RPE fluid becomes worse (relative to the visit when treatment was suspended) on OCT.

6.0 Trial measures

The Merlot Trial is designed to test the hypothesis that epimacular brachytherapy will reduce the frequency of Lucentis® retreatment that patients require, whilst maintaining visual acuity.

Efficacy of the VIDION® System will therefore be assessed with respect to its ability to prevent loss of visual acuity and its ability to reduce patients' reliance on 'as required' Lucentis® injections.

6.1 Superiority co-primary outcome

This is the number of 'as required' re-treatment injections of Lucentis® per year. Where injections are not recorded as being present, these will be assumed to be absent. There will be complete data on this outcome.

6.2 Non-inferiority co-primary outcome

This is the change from baseline to 12 months in the ETDRS Best-Corrected Visual Acuity score of the number of letters that are read on an ETDRS Chart. This change-score is the visual acuity score at 12 months minus that at baseline. A positive change indicates a gain in vision from baseline, whereas a negative result indicates a loss in vision.

The baseline score is obtained from the assessment performed at the visit when the subject is treated with the VIDION® Ophthalmic System or Lucentis®.

The score is measured for each subject at each monthly visit.

Some subjects will have missing data at the primary time-point of 12 months post baseline.

A related secondary outcome is the longer term change in visual acuity from baseline to 24 months.

6.3 Secondary efficacy outcomes measures

The secondary efficacy outcome measures over baseline to 12 months are:

Binary outcome variables:

- Loss of < 15 ETDRS letters
- Gain of ≥ 0 ETDRS letters
- Gain of ≥ 15 ETDRS letters

Continuous outcome variables:

- Change in total lesion size (by fluorescein angiography)
- Change in total CNV size (by fluorescein angiography)
- Foveal thickness (measured using OCT).

6.4 Safety outcomes

Categorical safety outcome variables:

- Cataract AE
- Adverse Events by severity (AE)
- Incidence of AEs; Ocular AEs.

Time to event safety outcome variables:

- Safety Assessment Incidence
- Incidence of cataract changes
- Incidence of radiation induced toxicity

6.5 Timing of measures

After the baseline visit, there are monthly visits up to the 24 Month visit, and a further 36 Month visit for safety evaluation.

A schedule of visits is provided in the protocol.

For the effectiveness measures, re-treatment injections are recorded and ETDR scores are measured each on a monthly basis at visits.

6.6 Final assessment

The final assessment for safety is 36 months after baseline, and the effectiveness measures are collected up to 24 months post baseline.

6.7 Participant duration of study

The duration of study is one year for the effectiveness evaluation for the main paper for which this Plan applied. Participants are involved for two further years for further evaluation of longer term efficacy and safety evaluation.

7.0 Sample Size

7.1 Determination of the visual acuity margin

This is described fully in the protocol. A margin of 5 letters was used. If visual acuity is no more than 5 letters worse when brachytherapy is used over and above Lucentis, then the use of brachytherapy is defined to produce non-inferior visual acuity. In the trial sample, it is the entire 95% confidence interval that is required to lie above the margin of no more than 5 letters worse.

7.2 Determination of the visual acuity outcome variability.

This is described fully in the protocol. An estimate from the Pronto trial of 14.6 was used for the standard deviation.

7.3 Clustering of outcomes from eyes within subjects

Only one eye per subject can be selected for the study. For patients with both eyes eligible, the patient chooses which will be the study eye in consultation with the clinician. There is therefore no issue of clustering, where more than one eye is contributed to the primary study dataset. All observations are therefore able to be assumed to be independent in the sample size calculation and statistical analysis.

7.4 Determination of the sample size based on the visual acuity outcome

The sample size was set to be 363 subjects (1 eye per subject). The target of 330 followed up with primary outcomes was increased by 10% to allow for dropout. For a 2:1 allocation ratio, this meant that 220:110 are expected to be followed up.

These numbers would provide 90% power to declare non-inferiority with a 5-letter margin using a one-sided significance level of 5%, assuming the standard deviation of 14.6. The power drops to an acceptable 83% if a one-sided significance level of 2.5% is used. This is equivalent to assessing the (two-sided) 95% confidence interval against the margin, as required by regulators (CPMP, 2000).

7.5 Power to detect effects on number of injections.

This is described fully in the protocol.

The effect size was a between-arm difference in means of 2 injections per year, assuming 8 in the control group and 6 in the treatment group with respective estimates for the standard deviation of 4 and 3. The corresponding pooled standard deviation (using 2:1 ratio for T:C) is 3.37.

There is more than 99% power to detect a reduction in the mean number of injections per year of size 2.0. The study size provides 90% power at the 5% significance level to detect a reduction in injections of 1.3 per year.

7.6 Detectable effects sizes for secondary outcomes

For continuous outcomes, the sample size allows detection of small to moderate standardised effect sizes; there is 92% power with to detect standardised effect sizes of 0.4 SD between arms.

For binary outcomes, the sample size allows detection of moderate to large difference in proportion effect sizes, when the proportion is the mid-range of 0.2 to 0.8; so that there is approximately 90% power to detect a difference in proportions from 0.1 to 0.25, and 0.4 to 0.6.

8.0 Randomisation, Subgroups and Confounders

8.1 Arms

Each participant will be randomised to one of two trial arms.

8.2 Method of allocation

Allocation to arm is by the method of stratification with 2:1 allocation ratio (brachytherapy:comparison) within blocks in strata defined by the cross-classification of the stratifiers.

The two stratifiers are:

- Lens status (phakic or pseudophakic), and
- Lesion type (classic, minimally classic, or occult).

8.3 Relative timing of randomisation

Once a patient's inclusion and exclusion criteria have been determined and entered into an electronic randomisation system incorporated in the electronic CRF system, then the patient is eligible for enrolment. The patient is then allocated to treatment Arm A or Arm B.

8.4 Subgroup variables

Randomised effects will be compared between categories of baseline subgroup variables lesion type Lesion type (classic, minimally classic, or occult), lesion size (cut-point 3.5), baseline visual acuity, and lens status (phakic, pseudophakic).

NICE (2012) has indicated cataract as an adverse event of brachytherapy amongst phakic patients, and so lens status will be a subgroup variable for the purpose of cataract sensitivity analysis. Specifically, randomised effects will be assessed within the pseudophakic group, as this subgroup is not subject to cataract.

9.0 Distributional considerations

9.1 Use of data transformation

It is not anticipated that any continuous outcomes will need to be considered for transformation because the sample size is reasonably large for group comparisons. If relevant and necessary a log transformation would be considered, provided that the inferences retain a sensible interpretation; in relative terms between arms.

If a log transformation were insufficient to make normality or constant-variance assumptions plausible, despite the moderate to large sample size, then the analysis would proceed to report means, of original or log transformed data, and between-arm differences in these along with 95% confidence intervals obtained using the nonparametric Bootstrap method described in Carpenter & Bithell (2000).

9.2 Defining Outliers

This section covers the approaches for identifying subjects who have outlying values recorded, and the actions to take to resolve these where possible through data correction or sensitivity analysis. It is unlikely that influential outliers will remain. However the process for this unlikely eventuality is described in advance.

A 'univariate outlier' is defined here as a data-point being at least four standard deviations from the mean of its distribution. This definition will apply to the transformed scale for those outcomes that have been log transformed. This applies to visual acuity at baseline, 12-month, and other timepoints.

Visual acuity is collected on a monthly basis. A 'bivariate outlier' is defined here as the difference between successive data-points being at least four standard deviations from then mean of the differences. Simple plots of successive pairs of serial measures will be used through the 24-month period. The range across time will also be used as an indicator to screen for unusual values to be checked.

9.3 Handling outliers

Outliers will be queried for checking at this stage to confirm that they have been recorded correctly and the value is actually possible for anyone to achieve, or possible for the specific subject given previous values of the outcome and/or other outcomes which are known to be related. This may lead to a correction being identified, or replacement by missing value for those impossible values.

Importantly, the analysis (which may be adjusted for stratifiers and baseline) will proceed by retaining the remaining outliers in the principal analysis.

Then, secondarily, sensitivity analysis will be employed, which involves a robust approach in which outliers are excluded. If there is no 'material difference' in conclusions, then the analysis retaining outliers will be reported alone. Otherwise the result from sensitivity analysis will be noted.

A material difference in conclusions would include an alteration in p-value from one side of a critical value (e.g. $p=0.05$) to the other, or a 'non-negligible' alteration in the amount of standard errors that the treatment effect size may have altered. The expected change in standard error from a reduction in sample size will provide a benchmark.

If there is such a 'material difference' then an unadjusted corresponding nonparametric analysis will be undertaken. Compared with the p-value from this, if the p-value from the unadjusted overall analysis is closer than that from the unadjusted sensitivity analysis, then the adjusted sensitivity analysis results will be not be noted.

In the very unlikely event that there are any noted outliers with such influence, independent advice (such as from the TSC or other relevant research expert) may be taken for resolution, or footnoted sensitivity analysis results will be footnoted to the relevant table in the main paper.

9.4 Model assumptions

Assumptions of normality and constant variance for linear regression models (such as for visual acuity at 12 months, between arms) will be examined using residual and other diagnostic plots.

However, for between-arm comparisons in means of groups (as opposed to regression models to predict for individuals) it is the sampling distribution of the difference in means that needs to be assumed to be sufficiently consistent with a normal distribution, rather than the distribution of subject values.

In other words, evidence against a normality assumption would be taken more seriously for predictive cohort analyses than for estimation of between-group mean differences in this main trial paper. This is especially relevant given that the MERLOT trial has a large expected analysis sample size ($N=330$). In this situation, the effect of the central limit theorem is to produce sampling distributions for treatment comparison statistics to tend to a normal sampling distribution.

Therefore the principal comparisons of means and proportions are expected to be valid.

10.0 Descriptive analysis

10.1 Flow diagram

Recruitment, randomisation and follow-up for MERLOT will be summarised by arm in a CONSORT flow-diagram.

This will include the main reasons for there being missing data (withdrawal, lost to follow up) by stages of the trial, and will also include the numbers for whom this occurs per arm.

Also included will be the number randomised, who comprise the intention to treat trial population, and the numbers followed-up to be in the analyses of the co-primary outcomes.

10.2 Baseline comparability of randomised groups

The baseline characteristics of subjects will be summarised in each arm. For continuous descriptors, preferentially the mean(SD) will be used unless a median(IQR) would provide a more representative summary. Percentage(number) will be used for categorical descriptors.

The characteristics will include socio-demographic descriptors (including sex and age), randomisation stratifiers, baseline visual acuity and other clinical measures, severity of AMD, extent of prior use of Lucentis® or Avastin®.

This will allow a visual assessment of whether the randomisation procedure succeeded in producing comparable arms, and will not include the improper use of p-values from statistical hypothesis testing between arms at baseline.

This will also show baseline characteristics of the trial sample for description in the main paper.

10.3 Comparison of rates

Rates and proportions, such as the follow-up rate (percentage lost to follow-up) or cataract incidence (percentage developing one in the study eye) within 12M or 24M, will be reported for each arm. These will be compared between arms with p-values from univariate statistical tests: Pearson's chi-squared test or Fisher's exact test.

11.0 Analysis covariates

11.1 Stratifiers

It is important to consider which if any covariates are to be adjusted for in the analyses. The ICH E9 guideline (1998) recommends considering factors on which randomisation has been stratified. These factors tend to be predictive of outcome, and

therefore their adjustment as covariates will improve the precision of the estimated treatment effects.

11.2 Baseline

The corresponding baseline measure for a continuous outcome is also often predictive of the outcome at follow-up. Therefore 'baseline', if collected, will be an additional covariate when modelling continuous outcomes.

If there is missing data in the baseline of a continuous outcome, then this will be accommodated using the missing indicator method of White and Thompson (2005). This will only apply to secondary outcomes, as there is no baseline for injections, and any missing baseline ETDRS visual acuity score will be replaced by the screening score, present because it is required for declaring eligibility.

12.0 Analysis of co-primary outcomes

For each co-primary outcome, the mean will be used to summarise the point estimate of effect across participants in each arm.

12.1 Injections

A linear regression framework will be used. The number of 'as required' injections in the first 12 months will be the dependent variable, which consists of a count over the 12 injections at month 1, 2, ..., 12 post-randomisation. The independent variables will be the study arm, and the two randomisation stratifiers (lens status and lesion type).

The intention is to include all randomised subjects in this intention to treat analysis, without having to consider a reduced set of participants (modified ITT) unless strictly necessary.

The adjusted difference in the mean change-score between arms (treatment minus control) will be calculated as an estimate of the population efficacy. The 95% confidence interval for the difference will also be estimated. If the 95% confidence interval (two-sided) lies entirely above the margin of -5, then non-inferiority will be declared.

A sensitivity analysis will be undertaken in which those who have not attended any visits (from baseline onwards) are removed.

As the 'as required' injections are more likely to begin towards the early part of the 12-month period than the end, no correction will be made for those participants withdrawing early.

Non-attendance at any visit, and withdrawal rates will be calculated per arm and compared between arms.

12.2 Visual Acuity

A linear regression framework will be used. The change from baseline to 12 month ETDRS score will be the dependent variable. The independent variables will be the study arm, the two randomisation stratifiers (lens status and lesion type), and the baseline ETDRS score.

Some participants will have missing data at 12-months. For the intention to treat analysis, multiple imputation will be used; ten values will be imputed for each participant who is missing the 12-month score to produce ten complete datasets. The ten treatment effect estimates and standard errors (resulting from the ten linear regression analyses of the ten datasets) will be averaged using Rubin's rules described in Shafer (1999), in order to provide an overall treatment effect estimate with a standard error that is properly inflated to incorporate uncertainty associated with imputing values (i.e. between-imputation variability in the estimated treatment effect).

An alternative method – Last Observation Carried Forward (LOCF), which was used as the primary approach in the CATT trial – is a specific case of the general method of simple imputation (e.g. primary approach in the CABERNET trial) in which the imputed value is regarded as the genuine unobserved (missing) value with complete surety – on the same basis as values observed in other participants. On the other hand, multiple imputation is a method which incorporates uncertainty through the use of multiple varying imputations. This is important in avoiding underestimated standard errors, and for avoiding bias associated with LOCF. When there are very few participants with missing data (e.g. CATT trial), the methods provide similar results. LOCF and simple imputation will not be used.

More details on the steps taken within the multiple imputation approach are now given here.

Those participants who have both a baseline and a 12-month outcome will be used to estimate the relationship – **regression coefficients** - between visual acuity score at 12 months and visual acuity for other selected combinations of timepoints at which visual acuity is observed (e.g. 11-month and 13-month). The estimates (linear regression model coefficients, and residuals) will be used to impute multiple values of 12-month visual acuity in whom this is missing.

As a specific example, if a participant's baseline, 11-month and 13-month scores are observed, then the missing 12-month score will be imputed from multiplying these scores by the regression coefficients which relate these to the 12-month score.

More generally, those participants with at least one observed visual acuity score each side of 12 months, will have their score predicted from the specific linear regression model that draws on visual acuity scores at these two timepoints and baseline. Where there is more than one available timepoint to one side of 12 months, the timepoint closest to 12 months will be used.

Those participants with visual acuity scores observed only one side of 12-months will employ the linear regression coefficients relevant to the two timepoints closest to 12 months, and baseline. If fewer than two visual acuity timepoints are observed, then one, or failing that none, will be used in addition to baseline.

The ten multiple values imputed per participant with missing 12-month visual acuity score will be obtained by randomly selecting ten residuals from the relevant predictive linear regression model to add to the expected value predicted from the model.

Baseline ETDRS visual acuity, lens status and lens type will be present in all prediction models. This matches their presence in the main analysis. Importantly, the approach will be applied separately within each arm.

For those participants without a baseline score, the screening visual acuity score will be used instead.

12.3 Sensitivity analysis for primary outcomes

White et al (2011) have developed the concept of the “ITT strategy”, as opposed to “ITT analysis”. The strategy approach incorporates two analyses, one of which includes data from all randomised patients (ITT population) and the other of which does not necessarily need to do so. The point of having two analyses is to assess the influence of assumptions in terms of how the missing data is handled.

The primary method is multiple imputation, exploiting the visual acuity measures available at timepoints close to the missing 12-month one. Therefore adopting White’s strategy, a secondary so-called ‘complete case’ analysis will be undertaken, as was the case in the ABC trial (Tufail et al., 2010). Those participants with a missing 12-month visual acuity score will be therefore be omitted from this secondary analysis. Those participants with missing injection denominator data due to early withdrawal will be omitted for the ‘complete case’ analysis of injections.

These ‘complete case’ analyses are based on an assumption that the data was ‘missing completely at random’ for those participants excluded with missing data. In other words, the missing data is assumed to be unrelated (unpredictably) to any observed data from the participants. Alternatively, the primary multiple imputation approach is based on a less strong assumption that the data was instead missing just ‘at random’. In other words, some observed covariates (e.g. 11-month and 13-month scores) are useful in predicting the missing data (e.g. 12-month score) and once this predictive value is incorporated, then the remaining uncertainty is assumed to be unpredictable (‘at random’).

12.4 Conditions for testing for superiority

This study is designed to test for non-inferiority of brachytherapy relative to Lucentis® monotherapy. If non-inferiority is shown then it will be possible to proceed to test for superiority following the approach outlined in CPMP (2000), where ITT analysis is of primary importance.

13.0 Analysis of secondary outcomes

Secondary efficacy parameters will be compared between the two treatment groups using the 12 month timepoint:

13.1 Continuous outcomes

Examples of continuous secondary outcomes to be compared at 12-months between arms are:

- Change in total lesion size by fluorescein angiography,
- Change in total CNV size by fluorescein angiography,
- Foveal thickness measured using OCT.

They will be reported using means, and analysed using linear regression with arm as covariates and additional adjustment for the randomisation stratifiers and the baseline of the outcome. Where the baseline value is missing, then the White and Thompson (2005) method will be used.

13.2 Binary outcomes

Examples of binary outcome variables are:

- Loss of < 15 ETDRS letters
- Gain of ≥ 0 ETDRS letters
- Gain of ≥ 15 ETDRS letters

They will be reported using proportions and differences in proportions, by using the Cochran–Mantel–Haenszel test across the six strata formed by cross-classifying the two randomisation stratifiers.

13.3 Baseline Subgroups

The randomisation stratifiers Lens status and Lens type have a randomised basis as subgroup variables because stratified randomisation was used. Subgroup analysis will proceed by adding the subgroup variable and its interaction with arm to the regression analysis of the primary outcomes, with assessment of the interaction term. A forest plot will be used to display the estimated randomised effects (and 95% confidence intervals) within the categories of the subgroups variables.

13.4 Presentation

Results will be presented in tables and graphs. Visual acuity will be presented across time in each arm by using a line, from joining up the adjusted mean value at each monthly timepoint, including baseline. A 95% confidence interval will be added to each point. The means and confidence intervals will be obtained from a mixed effect model of visual acuity over time (full category terms) interacting with study arm, further adjusting for randomisation stratifiers but without baseline visual acuity. The plot may be translated to start from a mean of zero at baseline.

14.0 Cataracts

14.1 Importance

A much higher percentage of eyes in the brachytherapy treatment arm (25% in first year) are expected to develop cataract compared with the Lucentis® monotherapy arm.

In the CABERNET trials, cataract formation occurred in 48% of patients in the epimacular brachytherapy arm, which was suspected to be due to vitrectomy procedures. The trial included treatment-naïve patients, whereas MERLOT includes previously ranibizumab-treated patients

In the protocol, emphasis is on the importance that any visually significant cataract is treated prior to the key milestones for data collection at Month 12 and 24. To this end, a formal masked assessment of lens opacity (graded using the LOCSII system) has to be undertaken at Months 6 and 9, and at 18 and 21, in both treatment subjects and controls. If cataract surgery is deemed appropriate then this should be undertaken at least four weeks prior to the end of year visit (Month 12 and 24). Development of visually significant cataract can also be assessed for surgery at other timepoints.

Surgery, which enables light to pass directly through the eye to the retina, has some risks but serious side effects are very rare.

14.2 Analyses

A strong predictor of cataract development is the lens status, because cataracts are confined to occur after brachytherapy in patients whose lens status is phakic (NICE, 2012).

Therefore a subgroup analysis will be performed for each of the two primary outcomes, whereby the interaction between arm and the subgroup variable lens status (phakic, pseudophakic) will allow a test for differential effect of brachytherapy in these two categories of the subgroup variable.

This test is randomisation-respecting because lens status is a randomisation stratifier; as within each of the two categories of the stratifier, permuted random blocks were used.

The subgroup analyses will be extensions of the primary linear regression analyses, where the interaction is added, and the covariates are otherwise unchanged. For the analysis of visual acuity, the ten imputed datasets will be assessed for these interactions, using Rubin's rules.

As this interaction test will have low power to detect anything but large effects and may not be specific enough for lens status to act as proxy for cataract, an additional analysis approach will be undertaken as follows.

For each co-primary outcome, it will be determined by how much the treatment effect would need to be altered for those having surgery within 12 months, in order for the overall conclusions of the trial to change. The size of the required alteration will then be assessed for plausibility.

15.0 Handling multiple comparisons

All study analyses will be based on tests that are two-sided, including the two-sided 95% confidence interval based non-inferiority analysis of visual acuity which is equivalently one-sided at the 2.5% level.

A 5% level of significance will be adopted for both primary outcomes, without increase to false positive rate.

Significance tests will be used sparingly and restricted where possible to addressing stated hypotheses.

Secondary outcomes, as well as the co-primary outcomes, will be summarised using an effect size with a 95% confidence interval. Interpretation for those secondary outcomes that do not directly address the stated study hypotheses, will be more cautious.

Those hypotheses that are based on analyses of subgroups of the intervention arm will particularly be interpreted carefully so as not to conclude strongly the absence of effect if non-significant associations are identified unless the 95% confidence interval is informatively narrow.

Results that are significant in isolation will be interpreted less strongly than sets of results that are mutually supportive, or which support corresponding primary outcomes, or which are supported in previous research findings.

16.0 Software

The principal software package will be SAS, with verification of results from syntax for selected analyses in STATA, R or SPSS.

17.0 References

CABERNET Trial Statistical Analysis Plan (2011) Wittes JT and Yu Z-F.

Carpenter J, Bithell J. (2000) Bootstrap confidence intervals: when, which, what? A practical guide for medical statisticians. *Statistics in Medicine* 19:1141-1164.

Catt Research, Group; Martin, DF; Maguire, MG; Ying, GS; Grunwald, JE; Fine, SL; Jaffe, GJ (2011). "Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration". *New England Journal of Medicine* 364 (20): 1897–1908. doi:10.1056/NEJMoa1102673

CPMP (2000): The European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products (CPMP). Points to consider on switching between superiority and non-inferiority. CMP/EWP/482/99. July 27, 2000. (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50003658.pdf.)

CPMP (2004): Committee for Proprietary Medicinal Products (CPMP): points to consider on adjustment for baseline covariates. *Statistics in Medicine* 2004;23(5):701-709.

ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials. Recommended for Adoption at Step 4 of the ICH Process on 5 February 1998. <http://www.emea.eu.int/pdfs/human/ich/036396en.pdf>

NICE (2012) June: <http://guidance.nice.org.uk/IPG415>

Schafer JL (1999) Multiple Imputation: a primer. *Statistical Methods in Medical Research* 8:3-15.

Schulz KF, Altman DG, Moher D, for the CONSORT group. CONSORT 2010 statement: updating guidelines for reporting parallel group randomised trials. *BMJ* 340:c332.

Tufail, A.; Patel, P. J.; Egan, C.; Hykin, P.; Da Cruz, L.; Gregor, Z.; Dowler, J.; Majid, M. A. et al. (2010). "Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study". *BMJ* 340: c2459. doi:10.1136/bmj.c2459

White IR, Thompson SG (2005). Adjusting for partially missing baseline measurements in randomized trials. *Stat Med.* 24:993-1007.

White IR, Horton NJ, Carpenter J, Pocock SJ. (2011) Strategy for intention to treat analysis in randomised trials with missing outcome data. *BMJ* 342:d40.

18.0 DMC monitoring

At six-monthly DMC meetings, masked data is reviewed concerning trial recruitment, randomisation balance, adverse events, withdrawal rates, and efficacy measures.

19.0 Acknowledgments

Thanks are especially due to the MERLOT trial team, DMC and TSC members, including Tim Jackson and Catey Bunce.

20.0 Amendments to Versions

Version 1.1 21st October 2012 – Developed From Research Protocol.

Current:

Version 2.1 28th November 2012 – Meeting with Tim Jackson and Catey Bunce

Principal amendments from previous version:

Addition of subgroup variables, including pseudophakic (cataract-free).

Confirmation of injections defined as the number occurring at the 12 Visits in the first year.

Future:

Version 3.1/2 DMC / TSC; on approval lodged with independent statistician

Principal amendments from previous version:

21.0 Appendix 1 – Record post blind-break

21.1 Record of data decisions

Date	Decision and basis

21.2 Record of analysis decisions

Date	Decision and basis