# FINAL STUDY REPORT

**Study Title:**

**Greater Manchester Avastin for choroidal Neovascularisation (GMAN) Trial**

**A 23-month randomised, masked, prospective phase IV study assessing the safety and efficacy of two alternative treatment regimes using Bevacizumab (Avastin™) to treat patients with subfoveal and juxtafoveal choroidal neovascularisation (CNV) caused by age-related macular degeneration (AMD).**

**REC Ref/ CTA No: 07/H0206/57**

**Chief Investigator: Professor Paul Bishop**

**Sponsor: Central Manchester University Hospitals NHS Foundation Trust**

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| **List of Principal Investigators and Sites** | Professor Paul Bishop<br><br>Manchester Royal Eye Hospital<br>Central Manchester University Hospitals NHS Foundation Trust |
| **List of Publications (or plans for publications) including those for patients (if applicable)** | Randomised controlled trial over 92 weeks using bevacizumab for the treatment of neovascular age-related macular degeneration comparing a treatment regime with 12 weekly regular injections to one with injections on an as-needed basis.<br><br>Manuscript to be submitted in Sept 2014 |
| **Study Start and End Dates** | 1st Feb 2008 - 31st May 2013 |
| **Study Design** | Non-inferiority design randomised controlled trial |
| **No. of Patients (planned and analysed)** | 330 patients planned<br><br>331 analysed |
| **Main inclusion/exclusion criteria** | **Inclusion criteria**<br>• Men or women of any ethnic background over the age of 50 years with AMD<br>• Subfoveal choroidal neovascularisation or juxtafoveal choroidal neovascularisation where laser would ablate the centre of the FAZ<br>• Predominantly-classic CNV<br>• Minimally classic or occult with no classic CNV lesion |

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| | composition where there is evidence of recent disease progression (i.e. vision loss, lesion growth on FFA, progression on OCT examination, new blood associated with lesion within the preceding three months)<br>• The total area of CNV within the lesion (including classic and occult components) must be greater than 50% of the lesion area as defined by FFA<br>• The BCVA letter score must be between logMAR 0.3 – 1.2 (approximately 6/12 to 6/96 Snellen equivalent)<br>• Patients must have completed study consent forms and must be willing and able to comply with all of the study protocols<br>**Exclusion criteria**<br>• Prior treatment to the CNV lesion<br>• Lesion components including fibrosis, haemorrhage or serous pigment epithelial detachment representing greater than 50% of the lesion<br>• Retinal pigment epithelial tear (rip)<br>• Active intraocular inflammation within one month of screening for study<br>• Active or suspected ocular or periocular infection<br>• Uncontrolled glaucoma in study eye (IOP of greater than 25 mmHg despite anti-glaucomatous medication)<br>• History of ocular surgery or YAG (yttrium aluminium garnet) laser capsulotomy within two months of screening for study<br>• History of allergy to fluorescein<br>• Any systemic medication that may interfere with the safety of the patient or is known to be toxic to the retina<br>• Uncontrolled hypertension<br>• Within one month of major surgery<br>• Pregnant and or lactating women<br>• Women of child-bearing potential (i.e. not sterilised or not post menopausal) who are unwilling to use effective contraception during the study and for 6 months after Bevacizumab treatment has stopped.<br>• Men with a spouse or partner with child bearing potential unless the participant has agreed to use condoms |
| **Investigational Medicinal Product** | Bevacizumab delivered by intravitreal injection. |
| **Duration of Treatment** | 92 weeks |
| **Primary and Secondary** | **Primary objectives:**<br>• To demonstrate that a treatment regime over 11 and 23 months where Bevacizumab is given monthly for three |

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| **Objective(s)** | months and then on a prn basis at three monthly intervals, the "**PRN**" treatment arm, is not inferior to a regime where Bevacizumab is given monthly for three months and then every three months irrespective of clinical symptoms and signs, the "**ROUTINE**" treatment arm, with respect to Best-Corrected Visual Acuity (BCVA) on a LogMAR scale.<br>• To evaluate the safety of intravitreal Bevacizumab as assessed by ophthalmic and vital signs evaluations and adverse events reports over 23 months.<br>**Secondary objectives:**<br>• Investigation of equivalence between two arms using additional measures of visual function including contrast sensitivity (CS), reading speed (RS), and radial deformation acuity (RDA).<br>• To evaluate the efficacy of the two Bevacizumab treatment regimes by changes in visual function (BCVA, CS, RS, and RDA) from baseline over 11 and 23 months.<br>• To determine the mean number of treatments required in the PRN treatment arm after month 2 and for the patients that require further treatments after month 2 the mean time interval until this retreatment is required.<br>• To investigate the correlation between BCVA and additional measures of visual function (CS, RS, and RDA), and assess the variability of these measures over time, to establish the clinical usefulness of these measures in determining change over time in patients with CNV.<br>• To evaluate the efficacy of the two Bevacizumab treatment regimes by measuring changes from baseline of optical coherence tomography (OCT) and fluorescein angiographic (FFA) parameters over 11 and 23 months.<br>• To explore the temporal changes in BCVA at months 1, 2 and 3 to evaluate the onset of treatment effect.<br>• To undertake pharmacogenetic studies to determine whether any variations in treatment response can be attributed to identifiable genetic variations. |
| **Endpoints/ Outcome Measure(s)** | Best corrected visual acuity (Primary) |
| **Statistical Methods** | Non-inferiority design randomised controlled trial. |
| **Conclusions** | The routine arm (with injections at least every 3 months after 3 one monthly loading doses) was superior to the prn arm (where injections were given on an as needed basis after the 3 monthly loading doses). |

Signature:

Date: 15th July 2014