LEAVO

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LEAVO: A Multicentre Phase III Double-masked Randomised Controlled Non-Inferiority Trial comparing the clinical and cost effectiveness of intravitreal therapy with ranibizumab (Lucentis) vs aflibercept (Eylea) vs bevacizumab (Avastin) for Macular Oedema (MO) due to Central Retinal Vein Occlusion (CRVO).

1 Background and clinical data

Retinal vein occlusion (RVO) is the second most common retinal vascular disease after diabetic retinopathy (1). Central retinal vein occlusion (CRVO) is characterised by retinal haemorrhages, venous dilatation and tortuosity in all four quadrants of the retina. Macular oedema (MO) secondary to CRVO is presumed to occur due to retinal hypoxia leading to local vascular endothelial growth factor (VEGF) upregulation, with resultant increased vascular permeability, macula oedema and haemorrhage. Approximately 6,860 people develop CRVO every year in England and Wales of whom 5,150 develop visual impairment and are potentially eligible for treatment (www.NICE.org) (2). Once established, visual impairment due to CRVO is typically profound with little tendency to improve spontaneously (3), the natural history arm of the Central Retinal Vein Occlusion study (4) showing no change in mean baseline visual acuity over 3 years. Without intervention permanent visual impairment is likely to occur.

Ranibizumab is a monoclonal antibody fragment that inhibits VEGF and was the first anti-VEGF therapy to demonstrate improved visual outcomes in patients with MO due to CRVO, CRUISE (3) & HORIZON (5) and is now FDA and EMA approved. Aflibercept is a fusion protein of the key domains of VEGF receptors 1 and 2 and human IgG Fc that blocks all VEGF-A isoforms and placental growth factor. It is FDA approved for CRVO based on the GALILEO (6) and COPERNICUS (7) studies. Bevacizumab is a monoclonal antibody against VEGF that is EMA licensed for the treatment of cancer but not for use in the eye. However, it has gained worldwide intraocular use for several eye conditions including MO due to CRVO.

Despite robust clinical trial evidence for the clinical effectiveness of ranibizumab and aflibercept and anecdotal reports of the efficacy of bevacizumab, there is no direct comparison between these three agents to determine their relative clinical effectiveness, required frequency of administration, side effect profile and cost effectiveness. This study will therefore compare the clinical and cost effectiveness of these three anti-VEGF therapies in the treatment of MO secondary to CRVO over the 2 year natural history of the disorder to allow an informed decision regarding the appropriate drug in terms of clinical and cost effectiveness for clinical practice.

2 Objectives

The objective is to compare the relative clinical and cost effectiveness of the anti-VEGF agents bevacizumab (investigational treatment), aflibercept (investigational treatment) and ranibizumab (standard care) in MO due to CRVO over 100 weeks.

The primary objective is to determine whether bevacizumab and aflibercept are each non-inferior to ranibizumab in treating visual loss due to MO secondary to central retinal vein occlusion at 100 weeks .

Secondary objectives include the difference between arms in mean change in best corrected visual acuity at 52 weeks, the proportions in certain pre-defined categorical visual outcome groups and anatomical outcomes at 52 and 100 weeks , and incremental cost-effectiveness ratios and occurrence of side effects at 100 weeks.

3 Trial design

This is a phase III randomised controlled double-masked non-inferiority clinical trial to evaluate the relative clinical and cost-effectiveness of intravitreal bevacizumab and aflibercept compared to ranibizumab in MO due to CRVO. 459 patients with MO due to CRVO in at least one eye will be randomised 1:1:1 to bevacizumab [1.25mg in 50ul] (Royal Liverpool) and aflibercept [2.0mg/50ul] and ranibizumab [0.5mg/50ul] all administered by intravitreal injection over 96 weeks (Fig. 1) and followed for 100 weeks. The study will be conducted across approximately 40 Ophthalmology centres in the UK.

After participant study eligibility has been confirmed, the date of the milestone visits at weeks 0, 12, 24, 52, 76 and 100 weeks will be calculated and agreed. Visits at weeks 4 and 8 will also be fixed. After week 12, all intervening follow up visits will be flexible and designed to fit around milestone visits. In the context of a non-inferiority study, the protocol is designed to be as flexible as possible to accommodate variations in normal clinical practice between individual investigators, following mandated injections at weeks 0, 4, 8 and 12. The protocol thus provides guidance on recommended treatment frequency but deviation from this schedule by utilising the wide visit windows and omitting treatment visits where visit 'slippage' has occurred, is permissible and not considered a protocol deviation.

4 Selection of Participants

4.1 Inclusion Criteria

1. Subjects of either sex aged ≥18 years.
2. Clinical diagnosis of centre-involving macular oedema (MO) due to CRVO
3. CRVO of ≤12 months duration.
4. Best corrected visual acuity in the study eye ≥19 and ≤78 ETDRS letters (approximate Snellen VA 3/60 to VA 6/9).
5. Best corrected visual acuity in the non-study eye ≥14 ETDRS letters (approximate Snellen VA ≥2/60).
6. SD-OCT central subfield thickness (CST) >320µm (Spectralis) predominantly due to MO secondary to CRVO in the study eye or equivalent CST in other SD_OCT machines.
7. Media clarity, pupillary dilatation and subject cooperation sufficient for adequate fundus imaging of the study eye.
8. In cases of bilateral CRVO, if both eyes are potentially eligible, unless the patient prefers otherwise the worst seeing eye will be recruited.

4.2 Exclusion Criteria

The following apply to the study eye only and to the non-study eye only where specifically stated:

1. Macular oedema considered to be due to a cause other than CRVO (e.g. diabetic macular oedema, Irvine-Gass syndrome).
2. An ocular condition is present that, in the opinion of the investigator, might affect macular oedema or alter visual acuity during the course of the study (e.g. vitreomacular traction)
3. Any diabetic retinopathy or diabetic macular oedema at baseline clinical examination of the study eye
4. Moderate or severe non proliferative diabetic retinopathy (NPDR) or quiescent, treated or active proliferative diabetic retinopathy (PDR) or macular oedema in the non-study eye. Note: Mild NPDR only is permissible in the non-study eye.
5. History of treatment for MO due to CRVO in the past 90 days with intravitreal or peribulbar corticosteroids or in the last 60 days with anti-VEGF drugs or >6 prior anti-VEGF treatments in the previous 12 months.
6. Active iris or angle neovascularisation, neovascular glaucoma, untreated NVD, NVE and vitreous haemorrhage or treatment for these conditions in the last 1 month.
7. Uncontrolled glaucoma [>30mmHg], either untreated or on anti-glaucoma medication at screening.
8. Any active periocular or intraocular infection or inflammation (e.g. conjunctivitis, keratitis, scleritis, uveitis, endophthalmitis).

Systemic exclusion criteria:

9. Uncontrolled blood pressure defined as a systolic value >170mmHg and diastolic value >110mmHg.
10. Myocardial infarction, stroke, transient ischaemic attack, acute congestive cardiac failure or any acute coronary event <3 months before randomisation
11. Women of child bearing potential unless using effective methods of contraception throughout the study and for 6 months after their last injection for the trial. Effective contraception is defined as one of the following:
    a. Barrier method: condoms or occlusive cap with spermicides.
    b. True abstinence: When it is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    c. Have had tubal ligation or bilateral oophorectomy (with or without hysterectomy).
    d. Male partner sterilisation. The vasectomised male partner should be the only partner for the female participant.
    e. Use of established oral, injected or implanted hormonal methods of contraception and intrauterine device
12. Pregnant or lactating women.
13. Males who do not agree to an effective form of contraception for the duration of the study and for 6 months after their last injection for the trial.

14. Hypersensitivity to the active ingredients aflibercept, bevacizumab or ranibizumab or any of the excipients of these drugs.
15. Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies
16. A condition that, in the opinion of the investigator, would preclude participation in the study.
17. Participation in an investigational trial involving an investigational medicinal product within 90 days of randomisation

5 Study procedures and schedule of assessments

5.1 Informed consent procedure

The Principal Investigator or designated sub-investigator will be responsible for taking full consent. Patients will be advised that any data collected will be held and used in accordance with the Data Protection Act 1998, given at least 24 hours after receiving the patient information sheet (PIS) to consider taking part and may be rescreened 2 weeks after an initial screen fail.

5.2 Randomisation procedures

A patient identification number (PIN) will be generated by registering the patient on the MACRO eCRF system (InferMed Macro), following consent. This unique PIN will be recorded on all source data worksheets and used to identify the patient throughout the study. Randomisation will be via a bespoke web based randomisation system hosted at the KCTU by authorised site staff who will be allocated a system username and password.

5.3 Masking

Masking of treatment allocation: the randomization process will inform only the pharmacy at the local trial site of the subjects' treatment allocation, with a copy to the emergency unmasking service (eSMS Global) and unmasked trial management staff. The clinical assessment team including the site PI, optometrist i.e. assessor of the primary outcome, site trial co-ordinator, the clinical investigator, clinical assessment study nurse, ophthalmic technician and patient will therefore remain masked throughout the study as there will be no record of the subjects' treatment arm in the source notes or case report form. Similarly, co-ordinators or administrators completing questionnaires in person with participants or in extreme circumstances only by telephone at specific time points will have details of subject study number only. Certain secondary outcomes e.g. interpretation of fluorescein angiography will occur at the remote NetwORC UK Reading Centre where assessors will be masked to treatment allocation. These masking procedures will avoid both performance and detection bias.

5.4 Study assessments

The flow chart of study assessments is shown in Table. 1.

5.4.1 Independent Reading Centres in NetwORC UK

The NetwORC UK will provide each site with a study imaging protocol, incorporated into the Manual of Operations giving instructions and guidance on how to acquire and transfer SD-OCTs, CFPs and FFAs to the Independent Reading Centres.

5.5 Treatment procedures

5.5.1 Treatment schedule

After mandated administration in all three study arms at baseline, 4, 8, and 12 weeks, further PRN intervention will be administered at weeks 16 to 20, with four week follow up and weeks 24 to 96, with 4 to 8 weekly follow up if the retreatment criteria are met and VA ≤83 letters.

Re-treatment criteria are met if one or more of the following is present:

1. a decrease in visual acuity of ≥6 letters between the current and most recent visit attributed to an increase in OCT CST OR
2. an increase in visual acuity of ≥6 letters between the current and most recent visit OR
3. OCT CST >320µm (Spectralis or refer to appendix 1) due to intraretinal or subretinal fluid OR
4. OCT CST increase >50µm from the lowest previous measurement.

From week 24 to week 96, intervals will initially be 4 weekly with the potential to increase to 8 weekly if criteria for 'Stability' are achieved. 'Stability' is defined as three successive visits from week 16 onwards at which Retreatment Criteria are not met and so the first time at which treatment could be deferred for 8 weeks is week 24. Similarly 'success' is defined as an ETDRS letter score >83 letters and if present at any retreatment visit from 16 weeks onwards, treatment should not be given at that visit and the participant reviewed in either 4 or 8 weeks depending on their pre-existing visit interval. If at any subsequent visit, Retreatment Criteria are met and BCVA ≤83 ETDRS letters then retreatment is commenced.

At each visit between weeks 24 and 96 inclusively, 'Non responder treatment suspension' criteria maybe met at any visit if the participant received an injection at the previous three visits and CST has not decreased by 50um compared to the highest value of CST in the previous 3 visits and visual acuity has increased or decreased ≤5 letters from the previous visit. If so, the PI or his designee at their discretion can suspend treatment to prevent therapy in a participant who has not responded to at least their last three injections. If the criteria for restarting therapy after 'Non-responder treatment suspension' are met, then the participant should resume therapy. Either of the following is a criteria for restarting therapy: (1) an increase or decrease in BCVA ≥6 letters between the current and any visit at or after the point of treatment suspension or (2) an increase or decrease >50um on OCT CST between the current and any visit at or after the point of treatment suspension.

A 'persistent non-responder' is defined as a participant who experiences ≤5 letter improvement in visual acuity AND <50um reduction in OCT CST compared to baseline at any assessment in the study at or after 24 weeks.

Treatment may be deferred in the following situations:

1. If an eye has experienced adverse effects from prior intravitreal injection, further retreatment with intravitreal agent is at the discretion of the investigator.
2. Treatment with anti-VEGF may be deferred in cases of total vitreous haemorrhage with no clear view of the fundus until the fundus can be sufficiently well visualised to permit subsequent intraocular injection.
3. Anti-VEGF injection may be deferred in an eye that has developed a rhegmatogenous retinal detachment or requires surgical intervention for any reason eg. tractional retinal detachment threatening the fovea. Anti-VEGF injections may be resumed following surgical intervention.
4. Anti-VEGF injections should be deferred if the interval between the current and previous visit is less than 4 weeks.
5. Anti-VEGF injection may be deferred in a visit where IOP remains above 30mmHg prior to injection despite the use of iopidine or other appropriate topical anti-glaucoma therapy immediately prior to the procedure. The participant may then be prescribed iopidine or other appropriate topical anti-glaucoma therapy for a week and rescheduled for anti-VEGF injection within a week if IOP is reduced to <30 mmHg. Even if this visit falls outside the visit window it will still be considered part of the same visit. At all other times, participants with elevated IOP will be managed with anti-glaucoma therapy at the discretion of the investigator that would reflect their normal clinical practice or according to local site policy.

5.6 Concomitant procedures

Either complete or sector panretinal photocoagulation to the study eye is permitted if an ischaemic CRVO or ocular neovascularisation is observed in any visit. A study eye in any arm may develop sight-threatening vitreous haemorrhage or retinal detachment. Anticipated need for cataract surgery in the study period is an exclusion criterion. Planned cataract surgery will be allowed in the study eye if in the opinion of the investigator it is visually significant. Other planned procedures may be required in the study and non-study eye. If macular oedema due to any retinal disease is present in the non-study eye, it is advocated that macular laser therapy be given as the first line therapy if appropriate. However, the participant can be treated with intravitreal anti-VEGF therapy or steroid therapy as per discretion of the treating physician. Diagnosis and treatment of endophthalmitis is based on investigator judgement and local hospital policy. Diagnosis and management of ischaemic CRVO, NVA, NVI, NVG, NVE and NVD in the study eye is based on investigator discretion and local practice. Laser therapy will form the mainstay of therapy and will be recorded as a concomitant procedure. Anti-VEGF agents in the study eye for NVG should be avoided.

6 Recording and reporting of adverse events and reactions

All SAEs, SARs & SUSARs shall be recorded and reported on the serious adverse event form to the Chief Investigator / delegate within 24 hours of learning of its occurrence.

7 Data management and quality assurance

The study will employ an eCRF created using the InferMed MACRO database system. Data will be managed via this system.

8 Statistical Considerations

8.1 Outcomes

8.1.1 Primary outcome

Change in best corrected visual acuity from baseline to 100 weeks in the study eye of all patients measured by ETDRS letter score at 4 metres.

8.1.2 Secondary Outcomes

8.1.2.1 Visual Acuity and Clinical Outcomes

1. Change in best corrected visual acuity ETDRS letter score measured at 4 metres between baseline and 52 weeks.
2. A ≥15 ETDRS letter improvement (appreciable visual gain), a ≥10 letter improvement, a <15 letter loss and a ≥30 ETDRS letter loss (severe visual loss) at 52 and 100 weeks.
3. A ≥73 ETDRS letters or better than 6/12 Snellen equivalent (i.e. approximate driving visual acuity), a ≤58 ETDRS letters (≤6/24) and a ≤19 letters (≤3/60)(CVI partial and severe visual impairment) outcome at 52 and 100 weeks.
4. The change in OCT CST and macular volume from baseline at 52 and 100 weeks.
5. OCT CST <320µm (Spectralis) at 52 and 100 weeks (key guide to subsequent NHS clinical practice).
6. The number of injections performed in the study eye at 100 weeks .
7. Changes in the area of non-perfusion at 100 weeks.
8. Changes in OCT anatomical features over time and at 100 weeks.

8.1.2.2 Patient reported and cost-effectiveness outcomes

Quality of life scales

(VFQ25 composite score, distance and near subscales, and EQ-5D with and without vision 'bolt-on') at 0, 12, 24, 52, 76 and 100 weeks.

Resource utilization (Client Service Receipt Inventories) at 0, 12, 24, 52, 76 and 100 weeks.

8.1.2.3 Safety and tolerability.

1. Occurrence of local and systemic side effects at 100 weeks.
2. Development at week 100 i. to become a persistent non-responder ii. of a change in retinal non-perfusion compared to screening iii. of anterior and posterior segment neovascularisation.

8.1.2.4 Pre-specified sub-group analyses

1. To determine differences between arms in mean change in best corrected visual acuity at 100 weeks across baseline subgroup variables defined by i) baseline visual acuity stratified as ≤38 letters, 39-58 letters, 59-78 letters, ii) duration of disease stratified as: <3 months, 3-6 months and >6 months, iii) treatment stratified as naïve vs previous treatment iv) quantity of retinal ischaemia (<10 , ≥10 and <30, and ≥30 DA of non-perfusion).

8.2 Sample size recruitment

8.2.1 Sample Size Calculation

Bevacizumab and aflibercept are hypothesised to be substantially inferior to ranibizumab, if in each case, the mean of the primary outcome (change in best corrected ETDRS visual acuity letter score) is worse by a margin of five letters , a previously used non-inferiority margin (10), representing the minimum VA change a patient may distinguish. For CRVO, Campochiaro et al. (3) reported a standard deviation of 14.3 in the ranibizumab 0.5mg arm. 12-month lost to follow-up was 8.4% in ranibizumab arms. In the absence of 24-month data, we have assumed a comparable standard deviation (SD) of 14.3 at 100 weeks, and allowed for 15% dropout. The two null hypotheses, that bevacizumab is substantially inferior to ranibizumab, and that aflibercept is substantially inferior to ranibizumab, will each be rejected if the estimated 95% confidence interval for the difference in treatment means lies wholly above the five letter margin in each case. Assuming equal efficacy, there will be 80% power to reject each null hypothesis and declare non inferiority with 130 followed-up patients analysed per arm. Allowing for 15% missing data at 100 weeks, 459 patients will be randomized to the three arms (equal allocation ratio; 153 per arm) for the CRVO patient group. Sample size calculations were performed using nQuery Advisor 4.0 software. The primary method of analysis will include all available refracted data of the primary outcome, at screening,12, 24, 52, 76 and 100 weeks, including data from the 15% of patients we anticipate could be missing the 100 weeks primary outcome endpoint, thereby giving flexibility to provide increased power or a higher dropout allowance for the stated power without having to amend the sample size in this event.

8.2.2 Primary outcome analysis

Analyses will be on an intention to treat (ITT) basis. The primary outcome will be compared between arms primarily at the 100-week point and secondarily at the 52-week point using a linear mixed effects model with

patient as a random effect to allow for within-patient correlation of repeated measures over time. The fixed effects will consist of arm, time, the continuous form of the baseline of the outcome, the missing indicator method, if required, the remaining randomisation stratifiers and the interactions of these with time. The test for non-inferiority will be one-sided at the 2.5% significance level, and presented as an estimated effect with two-sided 95% confidence interval compared against the non-inferiority margin. Treatment effect estimates and confidence intervals at a time point will be obtained directly from the model by setting that time point as the reference.

For the analysis of the primary outcome, the mixed effects model will be re-fitted in a reduced per protocol (PP) population, defined as the subset of patients found to be eligible at entry and who had minimal sufficient exposure to the treatment regimen, defined as 4 treatments correctly assessed and received during the first 6 visits up to week 20. For each of the first four visits, a correct treatment is defined as receiving the injection. For the 5th and 6th visits, a correctly assessed and received treatment is defined to be the receipt of an injection where this is indicated to be required by the retreatment criteria or the non-receipt of an injection where this is indicated by the retreatment criteria. Non-inferiority will only be concluded if this is declared by both the ITT analysis and the PP analysis at 100 weeks. Non-inferiority will also be assessed in ITT and PP populations at 52 weeks.

8.2.3 Secondary outcome analysis

Secondary outcome analyses will be on an ITT basis only, and assessed with tests at the two-sided 5% level of significance. Continuous outcomes will be compared between arms using a linear mixed effects model, as specified for the primary outcome ITT analysis, incorporating prior measurements of the outcome over time. Binary outcomes will be compared between arms using logistic regression. Continuous and binary outcomes will be reported as adjusted differences in means or odds ratios respectively. All tests will be two-sided at the 5% significance level and interpreted cautiously with a focus on interpreting effect sizes with 95% confidence intervals. Safety outcomes will be reported as unadjusted patient proportions and rates within and between arms with 95% confidence intervals using exact methods where appropriate.

8.2.4 Sensitivity and other planned analyses

Sensitivity to the missing at random assumption made in the primary outcome analysis will be undertaken to assess sensitivity to the handling of missing 100-week data, and to the use of concomitant treatments, and will be detailed in the statistical analysis plan.

If non-inferiority is concluded for either of the investigational treatments, then superiority will be assessed. If non-inferiority is concluded for both the investigational treatments then there will be a formal test of superiority to compare these two investigational treatments.

8.3 Randomisation methods

Only one eye can be randomised into the trial. In 95% of cases, one eye will be affected by CRVO and will be the 'worst seeing eye' and will therefore be randomised. On rare occasions, some patients may have bilateral

CRVO that meet the eligibility criteria. In these cases the worst-seeing eye will be randomised unless the patient opts for the 'better seeing eye' to be randomised.

459 adult patients with MO due to CRVO will be randomised 1:1:1 at the level of the individual using the method of minimisation incorporating a random element. The three stratifying factors are visual acuity (stratified by screening BCVA letter score (≤38 [approximate Snellen equivalent ≤6/60], 39–58 [approximate Snellen equivalent 6/48 to 6/24], ≥59 [approximate Snellen equivalent ≥6/18]), duration of disease from date of CRVO diagnosis to commencement of therapy (<3 months, 3-6 months and >6 months) and treatment naïve vs previous treatment.

8.4 Interim analysis

Formal interim analysis of the primary outcome for early stopping is not planned for this study. Regular interim reports will be prepared as needed for DMEC meetings.

8.5 Other statistical considerations

A detailed approved statistical analysis plan was completed prior to any randomisation and so prior to the availability of primary outcome data being supplied to the study statisticians.

9 Name of Committees involved in trial

9.1 Trial Steering Committee (TSC)

The TSC is the Committee, responsible for monitoring the overall integrity, conduct and safety of the trial. It will monitor its progress; investigate any serious adverse events; and take account of regular reports from the DMEC and communication from the TMG. . Ultimate responsibility for any decision required on the trial's continuation will lie with the TSC. The Committee will include an Independent Chair, a Professor of Statistics, an Independent Ophthalmologist and General Physician, Consultant in Public Health, Senior Department of Health Policy Maker, two principal investigators and two patient representatives. TSC meetings will take place at least annually. The TMG is the trial management group that meets regularly and deals with day to day running of the trial.

9.2 Data Monitoring and Ethics Committee (DMEC)

An independent DMEC of three persons, one Professor of Statistics and two Retina Specialists will meet regularly, to safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial. Its terms of reference are to receive and review the progress and accruing data of the trial and provide advice and recommendations on trial conduct to the Trial Steering Committee. The study may be prematurely discontinued on the basis of new safety information, or for other reasons given by the DMEC and/or TSC, Sponsor, regulatory authority or Research Ethics Committee concerned. All data reviewed by the DMEC will determine safety issues. All serious adverse reactions will be reported to the KCTU within 24 hours of learning of their occurrence.

10 Finance

The study is funded by the NIHR HTA CET – National Institute for Health Research, Health Technology Assessment Programme, Clinical Trials and Evaluation Stream. The funder ensures that they receive a study report periodically about the conduct of the trial and also receive the minutes of the TSC and DMEC meetings.

11 Indemnities

The participating NHS Trusts have liability for clinical negligence that harms individuals towards whom they have a duty of care. NHS indemnity covers NHS staff and medical academic staff with honorary contracts conducting the trial. There are no arrangements for non-negligent compensation.

12 Publication plan

It is planned to publish this study in peer review journals and to present data at national and international meetings. Results of the study will also be reported to the Sponsor and Funder, and will be available on their web site.

13 References

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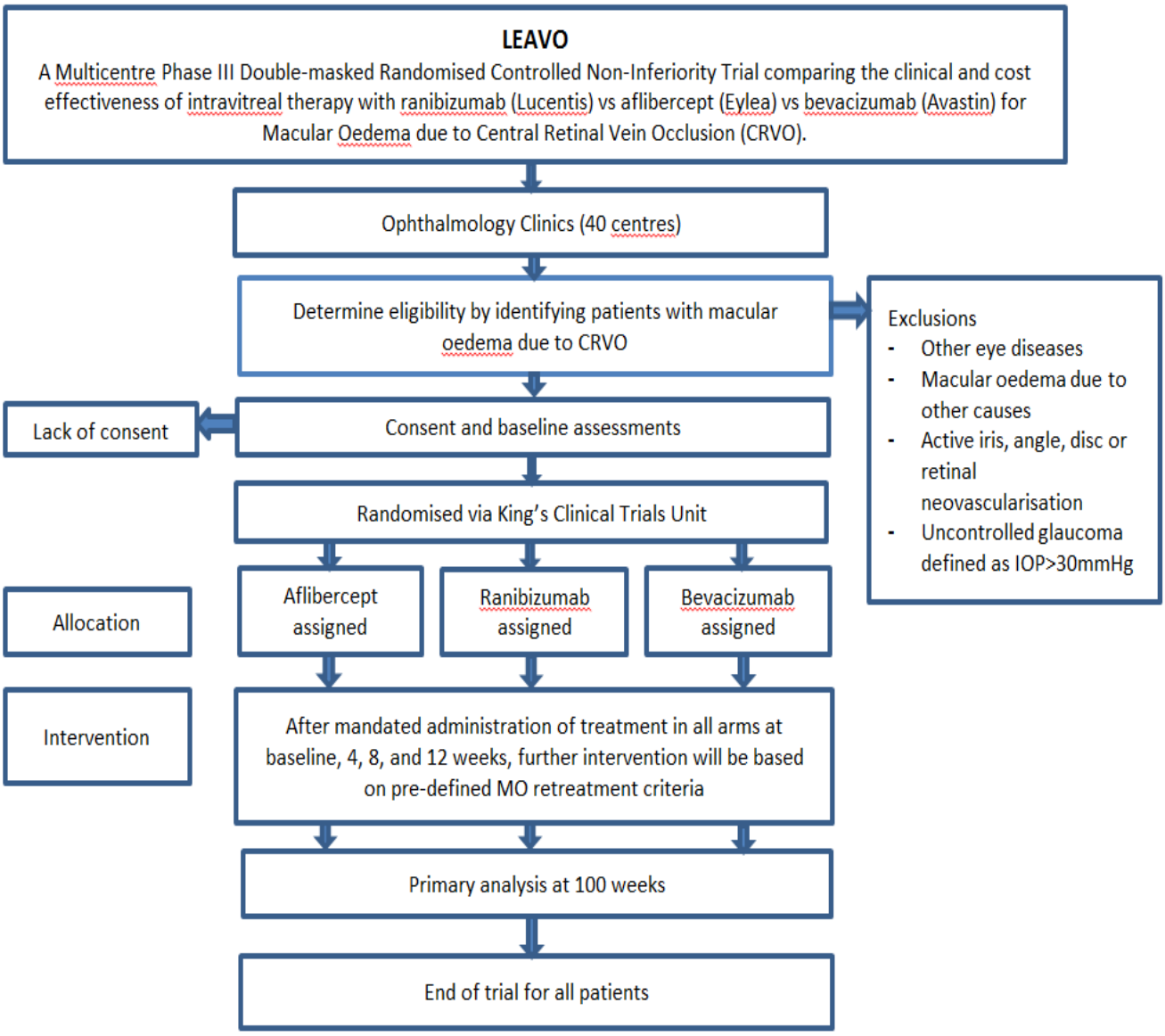
Table 1: Flowchart of study assessments

^Mandatory Visits: Loading (wk 4 & 8) & Milestones (baseline, wks 12, 24, 52, 76, 100)	Screening	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24		Week 52		Week 76		** Week 100	Unsch. Visit.	** Withdrawal Visit
Variable treatment visits									4-8 weekly		4-8 weekly		4-8 weekly			
Weeks		0	4	8	12	16	20	24	28-48	52	56-72	76	80-96	100	1-99	13-97
Visit window (days)	-10 to 0	0	0 to +14	0 to +14	0 to +14	-14 to +14	-14 to +14	-14 to +14	-14 to +14	-14 to +14	-14 to +14	-14 to +14	-14 to +14	-14 to +14		
Informed Consent	X															
Inclusion/Exclusion Criteria review	X	X[3]														
Randomisation[1]		X														
Urine Pregnancy test in women of child bearing age.	X															
Patient demographics, medical and ophthalmic history	X															
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Pressure	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Best corrected ETDRS visual acuity in both eyes (refraction visit =X1)	X1	X	X	X	X1	X	X	X1	X	X1	X	X1	X	X1	X / X1[5]	X1
Standard Ophthalmic Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SD-OCT in both eyes	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
7-field or wide-angle colour fundus photography[2]	X									X				X	+/-[5]	X
7-field or wide angle fundus fluorescein angiography[2]	X													x	+/-[5]	X
VFQ-25 and EQ-5D with and without vision 'bolt-on'		X			X			X		X		X		X	+/-[5]	X
Resource Use Questionnaire (CSRI)		X			X			X		X		X		X	+/-[5]	X
Treatment Allocation Guess Form[4]														X		X
Administer IMP*		X	X	X	X	X2	X2	X2	X2	X2	X2	X2	X2		X2	

X1 – Same day refracted best corrected visual acuity
X2 - PRN treatment.
Study Treatment Visit: non shaded square.
Study Milestone Visit: shaded square
^Milestone visits and mandated loading visit dates should be agreed with participant prior to performing randomisation
*Intravitreal injections including immediate post injection checks are performed as per each trial sites local policy and may include a check of ON perfusion or VA or IOP or a combination of these.
** Participants should be reminded to use an effective form of contraception for 6 months after their last trial injection. Females of child bearing potential should be reminded to notify the local study team if they fall pregnant during this time.
[1]Randomisation should only occur once all other assessments at baseline (week 0) have occurred
[2]Further colour fundus photographs and fluorescein angiography may be performed as per investigator discretion. Colour fundus photographs should be done if a patient converts from non-ischaemic to ischaemic CRVO.
[3]To include review of screening assessment test results and confirmation of eligibility
[4]To be completed by participants and masked site optometrists.
[5]To be performed (as required) if unscheduled visit is a milestone visit.

Figure 1: Consort diagram



Title

LEAVO: A Multicentre Phase III Double-masked Randomised Controlled Non-Inferiority Trial comparing the clinical and cost effectiveness of intravitreal therapy with ranibizumab (**L**ucentis) vs aflibercept (**E**ylea) vs bevacizumab (**A**vastin) for Macular Oedema due to Central Retinal **V**ein **O**cclusion (CRVO). (ISRCTN: 13623634)

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Background

Central retinal vein occlusion (CRVO) with macular oedema (MO) typically causes significant visual impairment untreated. Despite robust clinical trial evidence for the clinical effectiveness of the anti-VEGF agents ranibizumab and aflibercept and anecdotal reports of the efficacy of bevacizumab, all administered by repeated intravitreal injection, there has been no direct clinical trial comparison between these agents.

Aims

To compare the relative clinical and cost effectiveness of bevacizumab (investigational treatment), aflibercept (investigational treatment) and ranibizumab (standard care) in MO due to CRVO over 100 weeks.

Methods

Trial design

A phase III randomised controlled double-masked non-inferiority trial comparing intravitreal bevacizumab and aflibercept to ranibizumab over 100 weeks in MO due to CRVO in 46 UK Ophthalmology Centres.

Population

Patients of either sex, aged ≥18 years with MO due to CRVO of ≤12 months duration, study eye best corrected visual acuity (BCVA) ≥19 and ≤78 ETDRS letters (Snellen VA 3/60 to VA 6/9) and central subfield thickness (CST) >320μm on optical coherence tomography (OCT). The principal exclusion criteria are a co-existent ocular condition affecting BCVA and diabetic retinopathy.

Interventions

Intravitreal bevacizumab [1.25mg/ul], aflibercept [2.0mg/50ul] and ranibizumab [0.5mg/50ul] given by mandated injection at baseline, 4, 8, and 12 weeks, followed by 4 to 8 weekly PRN therapy if pre-specified re-treatment criteria are met and VA ≤83 ETDRS letters at all visits until week 96. Re-treatment criteria are a decrease or increase in BCVA ≥6 letters between the current and most recent visit, OCT CST >320μm or CST increase >50μm from the lowest previous measurement.

Outcome

The primary outcome is change in BCVA from baseline to 100 weeks in the study eye of all patients measured by ETDRS letter score at 4 metres. Secondary outcomes include local and systemic safety profile and occurrence of side effects at 100 weeks.

Sample size

Bevacizumab and aflibercept are defined to be inferior to ranibizumab, if in each case the primary outcome mean is worse by a margin of five letters. With a standard deviation of 14.3, the two null hypotheses are rejected if the estimated 95% confidence interval for the difference in treatment means lies wholly above this margin. Assuming equal efficacy, there will be 80% power to reject each null hypothesis and declare non inferiority with 130 followed-up patients analysed per arm. Allowing for 15% missing data, 459 patients in total will be randomized with equal allocation into three arms.

Analysis plan

Outcomes will be analysed on an intention to treat (ITT) basis. The primary refracted visual acuity outcome, and other continuous repeated measures, will be analysed using a model incorporating data over time. Non-inferiority will only be concluded if declared by both the ITT and an additional Per Protocol analysis of visual acuity at 100 weeks. Missing data will be accounted for in additional analysis. Mean costs and QALYs will be calculated, cost-utility analysis performed and incremental cost per QALY gained calculated. Pre-specified statistical and economic analysis plans have been independently approved.

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Date trial started: 12th December 2014

Expected end date: 31st August 2018.

Expected submission date: January 2019.