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The LEAVO study

Submission date 26/11/2014	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 26/11/2014	**Overall study status** Completed	
Last Edited 17/06/2021	**Condition category** Eye Diseases	

Plain English summary of protocol

Background and study aims
The retina is a light-sensitive layer at the back of the eye. It has a blood supply that provides oxygen and nutrients. Blood drains from the retina and leaves the eye through the central retinal vein. Blockage of the central retinal vein (CRVO) leads to fluid accumulating in part of the retina called the macula (macular oedema [MO]). This reduces the eye's ability to distinguish the details and shapes of objects (visual acuity). Until 3 years ago no treatment improved visual acuity in MO due to CRVO. The drugs ranibizumab and aflibercept are effective at improving visual function in patients with MO due to CRVO and cause relatively few side effects. Aflibercept may have a longer duration of action than ranibizumab but there is no data on the comparison for this condition. Bevacizumab, similar to ranibizumab, has been shown to be as good as ranibizumab for another eye disease, wet macular degeneration, and is significantly cheaper. Its use in MO due to CRVO would result in very significant NHS cost savings. However, more data is required to support its routine use for this condition in the NHS. This study will determine whether bevacizumab and aflibercept are as effective as ranibizumab at improving visual function in MO due to CRVO and sufficiently cost effective to merit their use.

Who can participate?
Patients aged over 18 with MO due to CRVO

What does the study involve?
Participants are randomly allocated to be treated with either bevacizumab, aflibercept or ranibizumab injected into the eye, and are followed up for 2 years.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
The study will take place in approximately 50 Ophthalmology Centres in the UK and will be managed by the King's Clinical Trials Unit.

When is the study starting and how long is it expected to run for?
December 2014 to November 2018

Who is funding the study?
NIHR CEAT Programme (UK)

Who is the main contact?
Mr Philip Hykin

Contact information

Type(s)
Scientific

Contact name
Mr Philip Hykin

Contact details
Moorfields Eye Hospital
London
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EC1V 2PD

Additional identifiers

Clinical Trials Information System (CTIS)
2014-000272-26

Protocol serial number
17808

Study information

Scientific Title
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 due to central retinal vein occlusion

Acronym
LEAVO

Study objectives
The primary hypothesis is that bevacizumab and aflibercept are as effective as ranibizumab in reducing visual loss from macular oedema due to central retinal vein occlusion.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee London - London Bridge, 04/09/2014, ref: 14/LO/1043

Study design

Multicentre Phase III double-masked randomised controlled non-inferiority trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Macula odema due to central retinal vein occlusion

Interventions
Intravitreal aflibercept and bevacizumab versus intravitreal ranibizumab

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Aflibercept, bevacizumab, ranibizumab

Primary outcome(s)
Change in best corrected visual acuity from baseline to 100 weeks in the study eye measured in ETDRS letter score at 4 metres: difference in means between bevacizumab and ranibizumab and between aflibercept and ranibizumab

Key secondary outcome(s))
1. Clinical effectiveness: multiple additional visual acuity and anatomical outcomes
2. Cost effectiveness outcomes

Completion date
30/11/2018

Eligibility

Key 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 ≤ 73 ETDRS letters (approximate Snellen VA 3/60 to VA 6/12)
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. See appendix 1 for equivalent CST value for alternative 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

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
463

Key exclusion criteria
Current exclusion criteria as of 13/08/2018:
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 previously documented diabetic retinopathy or diabetic macular oedema in the study eye 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:
11.1. Barrier method: condoms or occlusive cap with spermicides
11.2. 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
11.3. Have had tubal ligation or bilateral oophorectomy (with or without hysterectomy)
11.4. Male partner sterilisation. The vasectomised male partner should be the only partner for the female participant
11.5. 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

Previous 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 previously documented diabetic retinopathy or diabetic macular oedema in 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 >3 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 3 months.
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:

11.1. Barrier method: condoms or occlusive cap with spermicides
11.2. 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
11.3. Have had tubal ligation or bilateral oophorectomy (with or without hysterectomy)
11.4. Male partner sterilisation. The vasectomised male partner should be the only partner for the female participant
11.5. 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

Date of first enrolment
01/12/2014

Date of final enrolment
16/12/2016

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Moorfields Eye Hospital
London
United Kingdom
EC1V 2PD

Study participating centre
45 other centres
United Kingdom
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Sponsor information

Organisation
Moorfields Eye Hospital (UK)

ROR
https://ror.org/03tb37539

Funder(s)

Funder type
Government

Funder Name
NIHR CEAT Programme: Ref No: 11/92/03

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	29/08/2019	01/11/2019	Yes	No
Results article		01/06/2021	17/06/2021	Yes	No
Protocol article	protocol			Yes	No
HRA research summary			28/06/2023	No	No