



Treatments for macular oedema following central retinal vein occlusion: systematic review

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-004120
Article Type:	Research
Date Submitted by the Author:	26-Sep-2013
Complete List of Authors:	Ford, John; University of East Anglia, Public Health Clar, Christine; Warwick University, Warwick Evidence Lois, Noemi; Centre for Vision and Vascular Science, Barton, Samantha; BMJ Technology Assessment Group, Thomas, Sian; Warwick University, Warwick Evidence Court, Rachel; Warwick University, Division of Health Sciences Shyangdan, Deepson; University of Warwick, Warwick Evidence, Warwick Medical School Waugh, Norman; University of Warwick, Warwick Evidence
Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Ophthalmology, Public health
Keywords:	Medical ophthalmology < OPHTHALMOLOGY, systematic review, anti-VEGF, Central retinal vein occlusion, macular oedema

SCHOLARONE™
Manuscripts

Only

1
2
3 **Treatments for macular oedema following central retinal vein occlusion:**
4 **systematic review**
5
6
7

8
9 **Authors**

10 John A. Ford, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich, UK
11 Christine Clar, Warwick Evidence, University of Warwick, Coventry, UK
12 Noemi Lois, Centre for Vision and Vascular Science, Queen's University, Belfast, UK
13 Samantha Barton, BMJ Technology Assessment Group, London, UK
14 Sian Thomas, Warwick Evidence, University of Warwick, Coventry, UK
15 Rachel Court, Warwick Evidence, University of Warwick, Coventry, UK
16 Deepson Shyangdan, Warwick Evidence, University of Warwick, Coventry, UK
17 Norman Waugh, Division of Health Sciences, Medical School, University of Warwick, Coventry, UK
18
19
20
21
22
23
24

25 **Corresponding author**

26 John Ford
27 Norwich Medical School
28 Faculty of Medicine and Health Sciences
29 University of East Anglia
30 Chancellors Drive
31 Norwich, NR4 7TJ
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

48 **Protocol:** Not published

49 **Words:** 5750 words

50 **Key words:** central retinal vein occlusion, aflibercept, ranibizumab, bevacizumab, dexamethasone,
51 pegaptanib, triamcinolone, systematic review, anti-VEGF, macular oedema
52
53
54
55
56
57
58
59
60

Disclosure

No additional data available.

Abstract

Objectives

To review systematically the randomised controlled trial (RCT) evidence for treatment of macular oedema due to central retinal vein occlusion (CRVO).

Data sources

MEDLINE, EMBASE, CDSR, DARE, HTA, NHSEED, CENTRAL and meeting abstracts (January 2005 to March 2013).

Study eligibility criteria, participants and interventions

RCTs with at least 12 months' follow-up assessing pharmacological treatments for CRVO were included with no language restrictions.

Study appraisal and synthesis methods

Two authors screened titles and abstracts and conducted data extracted and Cochrane risk of bias assessment. Meta-analysis was not possible due to lack of comparable studies.

Results

Eight studies (35 articles, 1714 eyes) were included, assessing aflibercept (n=2), triamcinolone (n=2), bevacizumab (n=1), pegaptanib (n=1), dexamethasone (n=1) and ranibizumab (n=1). In general, bevacizumab, ranibizumab, aflibercept and triamcinolone resulted in clinically significant increases in the proportion of participants with an improvement in visual acuity of ≥ 15 letters, with 40-60% gaining ≥ 15 letters on active drugs, compared to 12-28% with sham. Results for pegaptanib and dexamethasone were mixed. Steroids were associated with cataract formation and increased intra-ocular pressure. No overall increase in adverse events was found with bevacizumab, ranibizumab, aflibercept or pegaptanib compared to control. Quality of life was poorly reported. All studies had a low or unclear risk of bias.

Limitations

All studies evaluated a relatively short primary follow-up (1 year or less). Most had an unmasked extension phase. There was no head-to-head evidence. The majority of participants included had non-ischaemic CRVO.

Conclusions and implications of key findings

Bevacizumab, ranibizumab, aflibercept and triamcinolone appear to be effective in treating macular oedema secondary to CRVO. Long-term data on effectiveness and safety are needed. Head-to-head trials and research to identify “responders” is needed to help clinicians make the right choices for their patients. Research aimed to improve sight in people with ischaemic CRVO is required.

For peer review only

Article summary

Article focus

To review the clinical effectiveness of pharmacological treatments for central retinal vein occlusion.

Key messages

Bevacizumab, ranibizumab, aflibercept and triamcinolone have demonstrated good short-term clinical effectiveness in randomised controlled trials for the treatment of macular oedema secondary to central retinal vein occlusion.

Dexamethasone and pegaptanib have shown mixed results.

Strengths and limitations of this study

A robust systematic review method was used which only included randomised controlled trials.

There were no head-to-head trials and there was a lack of long-term data on both effectiveness and safety.

Introduction

Central retinal vein occlusion (CRVO) is a vascular disorder of the retina with often catastrophic consequences to vision and quality of life.^{1,2} The incidence of CRVO increases with age; most individuals affected are 50 years of age or older.³ It has been estimated that there are around 80 new cases of CRVO per million population per year.^{4,5} Although CRVO most commonly affects one eye, in around 10% of patients the disease affects both eyes.² Approximately 20% of patients with CRVO will develop large areas of retinal non-perfusion (ischaemia).⁶ Furthermore, a small proportion (around 8%) of patients with non-ischaemic CRVO may convert into the ischaemic type during follow-up.⁶ Retinal ischaemia may lead to the development of neovascularisation in the retina, iris or anterior chamber angle. Complications of neovascularisation include vitreous haemorrhage and neovascular glaucoma.⁶ Currently there is no treatment for ischaemic CRVO other than that aimed at ameliorating the severity of complications, with treatments such as panretinal photocoagulation. Even with the use of current therapies, some eyes with ischaemic CRVO end up blind and painful and, ultimately, enucleation (removal of the eye) is necessary to provide comfort to patients.

Not all people with CRVO will require treatment and macular oedema will resolve in about a third of those with non-ischaemic CRVO.^{2,7} However most will need treatment and the number of options has increased in recent years. Laser photocoagulation has been for many years the standard therapy for patients with macular oedema secondary to branch retinal vein obstruction (BRVO).⁸ However, laser treatment was not found to be beneficial to those with macular oedema secondary to CRVO;⁹ for these patients, no therapeutic modalities could be offered. Recently, several studies have demonstrated the benefit of anti-vascular endothelial growth factor (VEGF) therapies and steroids for the management of patients with macular oedema secondary to CRVO.^{10,11} Steroids, such as triamcinolone and dexamethasone, have anti-inflammatory and anti-proliferative attributes (as well as some anti-VEGF effects) and therefore are primarily effective by reducing the oedema of the macula.¹² Anti-VEGF treatments, such as bevacizumab, ranibizumab, aflibercept and pegaptanib, inhibit vascular endothelial growth factor A. In CRVO there is an increase in vascular endothelial growth factor A which leads to neovascularization and oedema.¹³ In the UK, NICE has approved dexamethasone (in the long-acting form, Ozurdex) and ranibizumab (Lucentis) and an appraisal of aflibercept is currently underway. Bevacizumab is also used, but is not licensed for use in the eye; however this is because the manufacturer has never sought a licence, preferring to market ranibizumab. Triamcinolone has also been used off-licence.

1
2
3 An up-to-date review incorporating all drug treatments for macular oedema secondary to CRVO is
4 needed. The purpose of this study is to review systematically the randomised controlled evidence
5 for drug treatments of macular oedema secondary to CRVO.
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Methods

A systematic review was conducted. The following databases were searched: MEDLINE, MEDLINE In-process, EMBASE (all via OVID); CDSR, DARE, HTA, NHSEED, CENTRAL (all via The Cochrane Library); Science Citation Index and Conference Proceedings Citation Index-Science (via Web of Knowledge). In addition to the bibliographic database searching, supplementary searches were undertaken to look for recent and unpublished studies in the WHO International Clinical Trials Registry Platform and ophthalmology conference websites (American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology from 2010 to 2012).

Search strategy

An iterative procedure was used to develop two search strategies with input from previous systematic reviews.^{14;15} The first search strategy was designed to retrieve articles reporting RCTs or systematic reviews about CRVO published from 2005 onwards (the publication date of the first RCT on triamcinolone in Medline). Terms for retinal vein occlusion were included to ensure identification of articles in which both BRVO and CRVO were covered, but were reported separately. The second strategy focussed on retrieving articles where adverse events of relevant pharmacological treatments for CRVO were reported. This second search was limited by condition (age-related macular degeneration (AMD) or RVO), study type (RCTs, SRs or observational studies) and date (published from 2010 onwards). Searches were conducted in March 2013. The strategies used in each database are provided in appendix 1. Auto alerts of searches were set up to capture relevant articles published after the dates of the searches.

Reference lists from the included studies and identified systematic reviews were screened.

Inclusion and exclusion criteria

RCTs were used to assess the clinical effectiveness and adverse events.

Only RCTs examining pharmacological treatment compared with laser treatment, observation, placebo (sham injection) or another pharmacological intervention with at least 12 months follow-up were included. Comparisons of different doses of drugs were not included unless there was an additional comparator group as defined above. Studies including CRVO and BRVO were included

1
2
3 providing participants with CRVO were reported as a subgroup. Studies assessing treatments aimed
4 at restoring circulation to the occluded vein shortly after onset (<30 days) were excluded. There
5 were no language restrictions.
6
7
8
9

10 *Outcomes*

11
12 The primary outcome was visual acuity measured as mean change in best corrected visual acuity
13 (BCVA) or as proportion of patients improving by 15 ETDRS (Early Treatment for Diabetic
14 Retinopathy Study) letters or more. Secondary outcomes included mean change in macular thickness
15 using optical coherence tomography (OCT), quality of life and adverse events.
16
17
18
19
20

21 *Screening and data extraction*

22
23 Search results were screened independently by two authors (CC, JF and ST). Differences were
24 resolved through discussion or by consulting a third author (JF). Data were extracted by one author
25 (CC and DS) and checked by a second (ST, CC). Data extraction included inclusion/exclusion criteria,
26 baseline demographics, mean change in BCVA, proportion of patients with 15 letters improvement,
27 central retinal thickness (CRT) and adverse events. Risk of bias was assessed by two reviewers using
28 the Cochrane risk of bias tool.¹⁶
29
30
31
32
33
34
35

36 Meta-analysis was not possible because of a lack of comparable studies.
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Results

Search results

The study flow is shown in figure 1. The electronic searches yielded 518 records. 475 were eliminated based on information in the titles and abstract. The full text of the remaining 43 records was checked, and a further eight were eliminated. Reasons for exclusion included the trial being a commentary rather than an RCT, the study having no relevant comparison group (dose ranging only), the participants did not have macular oedema secondary to CRVO, or the interventions being ineligible (non-pharmacological). The remaining 35 records (including conference abstracts) reported on eight RCTs of six different pharmacological agents, and these were included in the analysis. The Geneva study (2010)^{11,17,18} technically consists of two RCTs, but as these were analysed and reported together, it was counted as one RCT in this analysis.

We also identified three relevant ongoing trials, one investigating minocycline (<http://clinicaltrials.gov/ct2/show/study/NCT01468844>), one investigating a combination of bevacizumab and triamcinolone (<http://clinicaltrials.gov/show/NCT00566761>), and one investigating ranibizumab (<http://clinicaltrials.gov/show/NCT01123564>).

Study characteristics

Detailed study characteristics of the included studies are shown in table 1.

Study design

Of the eight included RCTs, six were described as double-blind and seven were sham-controlled. All but one were multicentre. Only one was not funded by industry. Four trials were international trials, two came from the USA, and one each from Austria and Sweden. Six of the trials measured primary end-points at around six months (24 to 30 weeks), whereas two measured primary end-points at 12 months. Five studies reported follow-up data for up to 12 months, and two reported data for follow-up periods of up to two years.

Participants

The trials randomised a total of 1714 eyes (one eye per person). The number of eyes per study ranged between 60 and 437. Follow-up at the primary end-point ranged from 77 to 98% (generally over 90% in the intervention groups). The participants had a mean age of between 59.0 and 70.5

1
2
3 years, and between 36 and 49% were female. Only two studies reported mean duration of macular
4 oedema (4.3 and 4.9 months). Five studies reported mean time since CRVO diagnosis (range 2.4 to
5 2.9 months). Mean baseline BCVA was between 44 and 52.5 ETDRS letters, baseline CRT was
6 between 569 and 721 μm . In most trials, the focus was on macular oedema secondary to CRVO only,
7 but in the Geneva trial macular oedema secondary to BRVO and CRVO was included and only limited
8 data were available on the CRVO-only group.
9
10

11 12 13 *Interventions*

14
15
16 The Geneva trial (2010 ff.)^{11;17;18} compared a 0.35 mg (n=136) and a 0.7 mg dexamethasone (n=154)
17 intravitreal implant with sham treatment (n=147). After the initial 6 month study period, patients
18 could enter a 6 month open label extension, where they received a 0.7 mg dexamethasone
19 intravitreal implant.
20
21

22
23 The SCORE trial (2009 ff.)¹⁹⁻³² compared intravitreal injections of 1 or 4 mg of triamcinolone (~2
24 injections over 12 months, n= 92 and 91 for 1 and 4 mg respectively) with an observation group
25 (n=88). The ROVO trial (2013)³³ compared a single intravitreal injection of 4 mg of triamcinolone
26 (over 12 months, n=25) with radial optic neurotomy (n=38) or sham injection (n=20).
27
28

29
30 In the COPERNICUS trial (2012)^{34;35}, intravitreal injections of 2 mg of aflibercept (n=114) were given
31 every 4 weeks over 24 weeks to the intervention group and the comparison group received a sham
32 injection (n=75). During weeks 24 to 52, patients in both groups received aflibercept if they met
33 protocol-specified retreatment criteria, and received a sham injection if retreatment was not
34 indicated (3.9 standard error 0.3 injections in the sham group and 2.7 standard error 0.2 injections in
35 the aflibercept group); after the first year, patients continued in a one-year extension phase with as
36 needed dosing. In the GALILEO trial (2012)^{36;37}, intervention patients also received intravitreal
37 injections of 2 mg of aflibercept (n=103) every 4 weeks over 24 weeks, while the comparison group
38 was given sham injections (n=71). During weeks 24 to 52, patients remained in their original
39 treatment groups but received their allocated treatment as needed; beginning from week 52 to
40 week 76, both groups received the study drug every 8 weeks.
41
42
43
44
45
46
47
48

49 In a trial by Wroblewski and colleagues (2009)³⁸⁻⁴⁴, patients received 0.3 or 1 mg intravitreal
50 injections of pegaptanib sodium every 6 weeks for 24 weeks (n=33 and 33), compared with a sham
51 injection group (n=32). Patients were followed up to 52 weeks.
52
53
54

55 The CRUISE trial (2010 ff.)^{10;45;46} compared monthly injections of 0.3 or 0.5 mg of ranibizumab (n=132
56 and 130) over 6 months with sham injection (n=130). During months 6 to 12, all patients could
57 receive intraocular ranibizumab (previously assigned dose or 0.5 mg for the sham group) if they met
58
59
60

1
2
3 prespecified functional and anatomic criteria; after 12 months' follow-up patients could continue in
4 the HORIZON trial for another 12 months, where they were eligible to receive intravitreal injections
5 of 0.5 mg ranibizumab if they fulfilled prespecified criteria.
6
7

8
9 Epstein and colleagues (2012)⁴⁷⁻⁴⁹ conducted an RCT in which they compared patients receiving four
10 intravitreal injections of 1.25 mg of bevacizumab (n=30) over 6 months with patients receiving sham
11 injection (n=30). From 6 to 12 months, all patients received intravitreal bevacizumab injections every
12 6 weeks.
13
14

15
16 *Outcomes.* The primary endpoint of all but one study was the proportion with a gain of 15 or more
17 ETDRS letters. The primary endpoint of the remaining study was mean change in BCVA. Studies also
18 reported gains or losses of ETDRS letters at various cut-off points, absolute BCVA, CRT, and safety
19 parameters. The COPERNICUS, the GALILEO and the CRUISE studies also measured vision-related
20 quality of life (National Eye Institute Visual Functioning Questionnaire, NEI-VFQ).^{10;34-37;45;46} EQ5D was
21 also used in GALILEO.
22
23
24

25
26 *Ongoing studies.* Of the ongoing trials, the first (clinicaltrials.gov NCT01468844) is a 24 month
27 double-blind RCT from the USA. It set out to test the safety and effectiveness of minocycline as a
28 treatment for CRVO in around 20 patients with macular oedema secondary to CRVO. Both groups
29 received monthly intravitreal bevacizumab injections over three months (and afterwards as needed),
30 and the intervention group also received 100 mg oral minocycline twice daily over 24 months. The
31 second trial (clinicaltrials.gov NCT00566761) is an open-label RCT from Mexico in only around 10
32 patients assessing whether combined treatment with bevacizumab and triamcinolone is more
33 effective than bevacizumab alone. The combination group received 2.5 mg of bevacizumab plus 4
34 mg of triamcinolone as a first dose and then two doses of bevacizumab alone at monthly intervals,
35 while the monotherapy group received three monthly doses of 2.5 mg bevacizumab alone. Follow-
36 up will be 12 months. A third RCT from Hungary compares monthly injections of ranibizumab for
37 three months (and as needed thereafter) with Argon laser treatment in around 40 patients with
38 macular oedema secondary to CRVO. Follow-up will also be 12 months. The primary endpoint in all
39 studies is BCVA over 12 months.
40
41
42
43
44
45
46
47
48
49

50 51 52 *Risk of bias* 53

54
55 Details of risk of bias assessment are shown in Table 3.
56
57
58
59
60

1
2
3 Most studies (except GALILEO (2012) and Epstein 2012)^{36;37;47-49} adequately described the generation
4 of the allocation sequence, but only half the studies gave enough details to confirm adequate
5 allocation concealment. Most studies (unclear in the ROVO 2013 study)³³ used at least partial
6 masking, and most studies appeared to have had masking of outcome assessment. Intention-to-treat
7 analysis was used in all studies. Where reported separately for comparison groups, losses to follow-
8 up tended to be slightly higher for the control groups than the interventions groups (79 to 88.5%
9 follow-up in the control groups and 90 to 98% in the intervention groups). All studies appeared to
10 have been free of selective reporting. Most studies included a power analysis (not reported for the
11 CRUISE study)^{10;45;46}, but in two cases (the SCORE and the ROVO studies)¹⁹⁻³³ the numbers
12 randomised were considerably below the numbers indicated in the power calculations. As far as
13 reported, there were no significant differences between comparison groups in baseline
14 characteristics.

25 26 *Clinical effectiveness*

27
28 Detailed study results can be found in Table 2.

29
30 *Visual acuity.* Figure 2 shows the primary endpoint in most studies, which was the proportion of
31 participants with a gain of 15 or more ETDRS letters. As there were no significant differences in
32 visual acuity results between groups using different dosages of the given pharmacological treatment,
33 intervention groups were combined for the sake of the plot.

34
35 In the Geneva trial (2010 ff.)^{11;17;18}, treatment of macular oedema secondary to CRVO with a 0.7 mg
36 intravitreal dexamethasone implant resulted in a 0.1 letter gain in BCVA compared to a loss of 1.8 in
37 the sham group ($p < 0.001$). The difference persisted in the extension period where all patients
38 received the 0.7 mg dexamethasone implant. However, there was no significant difference in the
39 proportion of patients gaining or losing 15 letters at either 6 or 12 months (0.35 or 0.7 mg
40 dexamethasone). This may reflect the timing of peak effect at 90 days with dexamethasone.

41
42 In the SCORE trial (2009 ff.)¹⁹⁻³², patients in the triamcinolone groups lost significantly fewer ETDRS
43 letters (triamcinolone 1mg 1.2 letters loss, 4mg 1.2 letters loss and observation 12.1 letters loss)
44 over both 12 and 24 months than patients in the observation group. The proportion of patients
45 gaining 15 letters or more was also significantly larger in the intervention groups at 12 and 24
46 months (25.6% compared with 6.8% and 31% compared with 9%, respectively). The proportion of
47 patients receiving triamcinolone and losing 15 letters or more was smaller (25.6%) than in the
48 observation group (43.8%), but this difference was not statistically significant ($p=0.06$).

1
2
3 There was some overall improvement in BCVA in both intervention groups at 12 months in the ROVO
4 trial (2013)³³, (triamcinolone 20%, radial optic neurotomy 47% and sham 10%) however it was
5 unclear whether there were any statistically significant differences between the 4 mg triamcinolone,
6 the radial optic neurotomy, or the sham group. However, there were significantly more patients with
7 an improvement of more than or equal to 15 letters in the neurotomy group than in the sham group
8 (47% versus 10%), but no significant difference to sham after one dose of triamcinolone.
9
10

11
12
13 In both the COPERNICUS (2012)^{34;35} and GALILEO (2012)^{36;37} trials patients in the aflibercept group had
14 a significant improvement in BCVA at 6 months of 18 and 17.3 letters (compared to 4 letters loss and
15 3.3 letter gain in sham groups respectively), and this was maintained at 12 months and was
16 significantly greater than the improvements in the sham groups. This was paralleled by a significantly
17 greater proportion of patients (56.1% compared with 12.3% and 60.2% compared with 22.1%,
18 respectively) gaining 15 letters or more. Patients treated sooner after diagnosis (less than versus
19 more than two months) seemed to benefit more (in terms of proportion of patients with 15 letters
20 or more gain) in both trials.
21
22

23
24
25 The increase in mean change in BCVA with 0.3 mg pegaptanib compared with sham did not reach
26 significance at 30 weeks in the trial by Wroblewski and colleagues (2009)³⁸⁻⁴⁴, but there was a
27 greater increase in BCVA with 1 mg pegaptanib compared with sham (9.9 letter gain compare with
28 3.2 letter loss). These differences were not statistically significant at 52 weeks. There was no
29 significant difference between any of the groups in the proportion of patients gaining 15 letters or
30 more at 30 weeks, but significantly fewer patients in both dosage groups lost 15 letters or more than
31 in the sham group (6% compared with 31%).
32
33

34
35
36 In the CRUISE trial (2010 ff.)^{10;45;46}, mean change in BCVA was significantly increased in the
37 ranibizumab groups (no difference between doses) compared with the sham group at both 6 and 12
38 months (12.0 letters gained in the 0.5 mg group compared to 7.6 in the sham group). After the one
39 year extension with ranibizumab as needed in all groups, there was no difference between the doses
40 of ranibizumab at 24 months. The pattern was similar for the proportion of patients gaining 15
41 letters or more.
42
43

44
45
46 In the trial by Epstein and colleagues (2012)⁴⁷⁻⁴⁹, treatment with intravitreal bevacizumab, compared
47 with sham treatment significantly increased mean change in BCVA (14.1 letters gain compared to 2.0
48 letters lost) and the proportion of patients gaining 15 letters or more (60% compared to 20%) at 24
49 weeks. This difference was maintained in the extension period, even though both groups had been
50
51
52
53
54
55
56
57
58
59
60

1
2
3 receiving bevacizumab. Younger patients (<70 years) tended to have better visual outcomes than
4 older patients (>70 years).
5

6
7 *Central retinal thickness.* In the Geneva trial (2010 ff.)^{11;17;18}, no significant difference was found in
8 the reduction of CRT after 6 months' treatment in patients with macular oedema secondary to CRVO
9 with the 0.7 mg intravitreal dexamethasone implant (no data given for the 0.35 mg implant)
10 compared with sham.
11

12
13
14 In the SCORE trial (2009 ff.)¹⁹⁻³², CRT decreased in all study groups, but there was no significant
15 difference between groups at either 12 or 24 months. Similarly, there was no clear difference in the
16 proportion of patients achieving a CRT of less than 250 µm. CRT decreased in all comparison groups
17 in the ROVO trial (2013)³³, but there was no significant difference between groups.
18

19
20
21 Both in the COPERNICUS trial (2012)^{34;35} and in the GALILEO trial (2012)^{36;37} there was a significantly
22 greater reduction in CRT at 6 months in the aflibercept group than in the control group. However the
23 significant difference was maintained in the longer term only in the GALILEO trial, where patients
24 continued their assigned treatment up to 12 months. In the COPERNICUS trial, patients in the sham
25 group also received aflibercept in the extension period, which caused a similar decrease in CRT as in
26 the original intervention group.
27

28
29
30 After 30 weeks of treatment with pegaptanib (Wroblewski and colleagues 2009)³⁸⁻⁴⁴, differences in
31 decrease of CRT versus sham did not reach significance, but at 52 weeks, the decrease in CRT was
32 significantly greater in both the 0.3 mg and the 1 mg pegaptanib groups compared with sham.
33

34
35
36 After treatment with ranibizumab in the CRUISE trial (2010 ff.)^{10;45;46}, a significant reduction in CRT
37 was observed and significantly more patients achieved a CRT of 250 µm or less in the intervention
38 groups (no difference between doses) than in the sham group at 6 months. This difference did not
39 persist at 12 and 24 months because all groups received ranibizumab as needed.
40

41
42
43 In the trial by Epstein and colleagues (2012)⁴⁷⁻⁴⁹, treatment with intravitreal bevacizumab
44 significantly decreased CRT and the proportion of patients with no residual oedema (CRT <300 µm)
45 at 24 weeks, compared with sham treatment. When both groups received bevacizumab in the
46 extension period, similar decreases in CRT and increases in the proportion of patients with no
47 residual oedema were seen.
48

49
50
51 *Vision-related quality of life.* Vision-related quality of life (NEI-VFQ25) was significantly higher in the
52 aflibercept group, compared with sham injection, at 6 months in both the COPERNICUS trial (+7.2
53 compared with +0.8)^{34;35} and the GALILEO trial (+7.5 compared with +3.5)^{36;37}. In the COPERNICUS
54
55
56
57
58
59
60

1
2
3 trial, patients in the sham group who received aflibercept in the extension period had a similar
4 increase in vision-related quality of life as patients in the original intervention group by 12 months.

5
6
7 In the CRUISE trial (2010 ff.)^{10;45;46}, vision-related quality of life (NEI-VFQ) was similarly increased in
8 both ranibizumab groups and statistically significantly more than in the sham group at 6 months
9 (+6.2 compared with +2.8). At 12 months, with all groups receiving ranibizumab as needed, the
10 increases were similar in all three groups.

11
12
13
14 *Adverse events.* The 0.7 mg dexamethasone intravitreal implant caused significantly more increased
15 intraocular pressure (IOP) than sham treatment (30.1%, versus 1.4% in the control group) in patients
16 with CRVO in the Geneva trial (2010 ff.)^{11;17;18} (not reported for 0.35 mg). The incidence of cataract
17 was also slightly higher in the dexamethasone group but numbers were small because of the short
18 duration. There were no other differences in adverse events between groups.

19
20
21
22
23 In the triamcinolone group (especially 4 mg, SCORE trial 2009 ff.)¹⁹⁻³², there was a higher increase in
24 IOP, lens opacity onset or progression (at 12 months) and cataract surgery (12 to 24 months) than in
25 the control group. There were no other differences in adverse events between groups. A similar
26 tendency was seen in the ROVO trial (2013)³³.

27
28
29
30 Aflibercept did not appear to increase the incidence of ocular or non-ocular adverse events
31 compared with sham in both the COPERNICUS trial (2012)^{34;35} and the GALILEO trial (2012)^{36;37}.

32
33
34
35 In the trial by Wroblewski and colleagues (2009)³⁸⁻⁴⁴, adverse events in response to pegaptanib were
36 not reported in detail, but there do not appear to have been any serious ocular or systemic adverse
37 events.

38
39
40 After treatment with ranibizumab in the CRUISE trial (2010 ff.)^{10;45;46}, there were no consistent
41 differences in ocular or systemic adverse events between the intervention groups. None of the
42 ocular adverse events appeared to have increased substantially after all patients received
43 ranibizumab up to 24 months.

44
45
46
47 Epstein and colleagues (2012)⁴⁷⁻⁴⁹ did not report adverse events in response to bevacizumab in
48 detail, but the treatment appears not to have caused any serious ocular adverse events over 48
49 weeks.

Discussion

Statement of principal findings

Compared to control, intravitreal steroids and anti-VEGF therapies increase the proportion of patients whose vision improves by 15 or more letters in patients with macular oedema secondary to CRVO. The most effective drugs result in over 60% of patients gaining 15 letters compared to only about 20% of the control groups. RCT evidence demonstrates the short-term effectiveness of ranibizumab, bevacizumab, aflibercept and triamcinolone. Results from trials of dexamethasone and pegaptanib were mixed. Long-term evidence is awaited.

Strengths and limitations

A robust systematic review methodology was used. A broad search strategy was implemented, which included not restricting the search strategy with drug terms. Grey literature was searched by screening meeting abstracts from relevant conferences. There were no language restrictions. Two reviewers screened titles and abstracts and conducted data extraction and risk of bias assessment. Risk of bias was assessed using the Cochrane Risk of Bias Tool and was generally judged to be low or unclear. Only studies with one year follow up were included to exclude studies with very short follow-up RCTs were identified for all the new ophthalmological drugs, except for the steroid, fluocinolone.

The main limitation is the short duration of follow-up. The primary outcome for most trials was measured at 6 months, with an extension phase up to 12 months. Hence, it is not known whether the benefit of these treatments will be maintained long-term. Furthermore, potential side effects of these treatments may not be captured in these studies as a result of their short follow-up. Patients and clinicians would like sustained, life-long improvement in visual acuity, but of all included studies only one of them had a follow-up of over 24 months.

The sample size of some studies was small. For example, the evidence for pegaptanib and bevacizumab comes from studies with around 30 participants per arm which substantially increases the risk of a type II error. Only three trials included quality of life data, arguably one of the most important outcomes.

The proportion of participants and severity of ischemia within the trials was not clear. Whilst ischaemia is not mentioned in the inclusion/exclusion criteria of most studies, these participants

1
2
3 were unlikely included in these studies, especially if the diagnosis of ischaemic CRVO is based on
4 strict criteria. Furthermore patients were entered into the trials relatively soon after diagnosis (mean
5 4.3 to 4.9 months) and the it is not clear if the effects would be similar in patients who present with
6 long standing disease.
7
8

9
10 Another weakness was that patients were not asked at the of trials, what treatment they thought
11 they had received, which would have provided data on the success of masking of allocation.
12
13

14 In the case of dexamethasone, the results at six months were not as good as at 90 days, because of
15 the duration of action. Earlier re-treatment, at say 120 days, would have improved results, but many
16 clinicians might be reluctant to repeat injections of dexamethasone implant often because of the
17 large needle size and risk of adverse effects.
18
19

20 21 *Adverse events* 22

23
24 Results from the included studies clearly demonstrate that steroids (triamcinolone and
25 dexamethasone) are associated with clinically meaningful increases in IOP and cataract progression.
26 Anti-VEGF therapy ocular adverse events reported in the trials were similar in both placebo and
27 intervention arms.
28
29

30
31 There is limited evidence of the safety of these drugs specifically in CRVO, but it would not be
32 unreasonable to look to trials in neovascular age-related macular degeneration (AMD) and diabetic
33 macular oedema (DMO) for safety data, where there is more experience. The CATT trial, which
34 compared bevacizumab with ranibizumab in AMD, suggested that there was a higher incidence (RR
35 1.29 95%CI 1.01 to 1.66) of serious systematic adverse events (primarily hospitalisations) in the
36 bevacizumab arm.⁵⁰ Some have raised concerns about arterial thromboembolic events with
37 bevacizumab, but none of these has been demonstrated in the published literature.⁵¹⁻⁵⁴ Micieli and
38 colleagues (2010) undertook a systematic review of the adverse events associated with
39 bevacizumab. 22 studies were reviewed, representing 12,699 participants.⁵⁵ Adverse events in
40 patients treated with bevacizumab were cerebrovascular events (0.21%), myocardial infarction
41 (0.19%) and increased blood pressure (0.46%). Most of these represent the background burden of
42 disease in patients with advanced eye disease. The proportion of these directly attributable to
43 bevacizumab is likely to be very small. Campbell and colleagues (2012) undertook a nested case-
44 control study of over 7,000 cases and 37,000 controls.⁵¹ Ranibizumab and bevacizumab injection was
45 the exposure and cardiovascular events were the outcome. The authors found that ranibizumab and
46 bevacizumab were not associated with increased cardiovascular events.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Increased IOP has been associated with ranibizumab, bevacizumab and pegaptanib. Sustained
4 increased in IOP has estimated to be 5.5-6.0% with these drugs.^{56;57}
5
6

7 Robust evidence on the long-term safety of aflibercept is awaited.
8
9

10 11 12 *What do these results mean?* 13

14 Until very recently, patients with macular oedema as a result of CRVO could only be offered visual
15 rehabilitation and visual aids in an attempt to help them to deal better with their reduced vision and
16 its implications in their daily activities and quality of life. Their future is brighter now as new options
17 to treat macular oedema have become available. Triamcinolone is likely to be a cost-effective
18 treatment at least in selected groups of patients, such as pseudophakic individuals or those with pre-
19 existing cataracts that may require cataract surgery in the near future. The lack of a commercially
20 available licensed product for intraocular administration may restrict its use in clinical practice.
21
22

23
24
25
26 Some anti-VEGF therapies, including bevacizumab, ranibizumab and aflibercept, have been also
27 shown to be effective in short term studies for the treatment of patients with macular oedema and
28 CRVO. Bevacizumab has the advantage of having a low cost with an apparently similar effect to
29 other anti-VEGF therapies^{50;58;59} but there is some reluctance to use it as it is not licensed for use in
30 the eye. This has been seen in other eye conditions, such as AMD and DMO. Aflibercept, requiring
31 potentially fewer injections than other anti-VEGF agents, could represent an advantage to patients
32 and may relieve pressure on ophthalmology clinics. As more options have become available,
33 ophthalmologists will need to decide, together with their patients, which may be the best treatment
34 option for them based on their visual requirements and life circumstances. Health care systems will
35 need to evaluate the cost-effectiveness of these new treatments and support affordable ones. The
36 National Institute for Health and Care Excellence is currently appraising aflibercept. Policy makers
37 are left in a difficult position because of bevacizumab. It is cheaper than all other drugs⁶⁰ and
38 appears to be as effective, but is unlicensed and unlike ranibizumab and aflibercept does not have
39 evidence from large, well-funded RCTs in CRVO. The use of bevacizumab would result in
40 considerable savings for the NHS.
41
42

43
44
45
46 It is important to note that the evidence of benefit of these new therapies is likely to only apply to
47 patients with non-ischaemic CRVO. Although some patients with ischaemic CRVO were included,
48 these individuals are likely to have mild ischaemic CRVO. Thus, for patients with established
49 ischaemic CRVO, there are no proven treatments available and further research into this area is very
50 much needed.
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

What is the context of these results

Earlier systematic reviews identified limited evidence on the clinical effectiveness of treatments. A review by Braithwaite and colleagues (search date August 2010)⁶¹ on anti-VEGF agents identified one RCT^{10;45;46} comparing two doses of ranibizumab and one RCT³⁸⁻⁴⁴ comparing two doses of pegaptanib sodium versus placebo or no treatment. In both RCTs, the higher dose of the anti-VEGF significantly improved BCVA compared with sham injection in the short term (~6 months), but the effects in the longer term were unclear. Braithwaite and colleagues concluded that data from the two RCTs could not be synthesised because ranibizumab and pegaptanib sodium might not be directly comparable. Subsequent RCTs identified in this review also suggest benefit in ocular outcomes in macular oedema secondary to non-ischaemic CRVO for the anti-VEGFs bevacizumab, and aflibercept.^{34-37;47-49}

Gewaily and Greenberg reviewed the literature on intravitreal corticosteroids (search date November 2008) versus observation in macular oedema secondary to CRVO and identified no relevant RCTs.⁶² Results from two observational studies suggested that triamcinolone acetonide might be beneficial in the treatment of macular oedema secondary to non-ischaemic CRVO. However, as the authors of the review caution because conclusions are primarily drawn from small case series and case reports with short follow up. Results from the SCORE 2009 RCT corroborate the observational studies.¹⁹⁻³² The effects of triamcinolone acetonide in people with non-ischaemic CRVO without associated macular oedema are less clear. Data from four observational studies led Gewaily and Greenberg to conclude that intravitreal corticosteroids are associated with transient anatomical and functional improvements.

Immediate treatment aimed at relieving the blocked vein and surgical interventions were outwith the remit of this review. Antithrombotics, such as low-molecular weight heparin (LMWH), and fibrinolytics have also been found to benefit visual acuity in retinal vein occlusion with no associated macular oedema. Two systematic reviews^{63;64} identifying the same three RCTs in recent onset (≤ 30 days) BRVO or CRVO found that LMWH improved visual acuity compared with aspirin and that the associated benefit was larger in CRVO; only one of the three RCTs included people solely with CRVO. One review⁶⁴ also included one RCT comparing ticlopidine with placebo and two RCTs assessing intravenous fibrinolytic therapy followed by warfarin or aspirin with either haemodilution or no treatment. The authors of the reviews conclude that no definitive recommendations can be made on clinical effectiveness of LMWH in CRVO given the limited evidence available.

1
2
3 Radial optic neurotomy involves the performance of a radial cut using a microvitreoretinal (MVR)
4 blade through the lamina cribrosa, scleral ring and adjacent sclera at a selected point in the optic
5 nerve head with the goal of "decompressing" the scleral outlet (space confined by the scleral ring
6 and containing the lamina cribrosa, the central retinal artery, central retinal vein and the optic
7 nerve. The SCORE trial found radial optic neurotomy to be more effective than sham.
8
9
10

11 12 13 14 *Further research*

15
16 Large adequately powered RCTs comparing ranibizumab, bevacizumab, aflibercept and
17 triamcinolone are needed. Part of the problem is that the US the Food and Drug Administration
18 requires pharmaceutical companies to present data establishing a drug's safety and effectiveness.
19 Whilst this does not specifically require a placebo-controlled trial, it is the most efficient study
20 design for demonstrating effectiveness and safety. Clinicians and researchers are left with placebo-
21 controlled trials demonstrating effectiveness for individual drugs, but a lack of evidence to help
22 them decide which is best for their patients.
23
24
25
26
27

28
29 Given the cost of these treatments and the burden of repeated injections to patients and health care
30 systems, research aiming to predict "responders" would be useful as at present this is done by
31 therapeutic trial. Treatments could then be targeted to patients likely to benefit. Research is also
32 needed on the frequency and sequences of drugs. As other pathogenic pathways besides
33 inflammation and VEGF-mediated pathways may be implicated in the development of macular
34 oedema in patients with CRVO, these should be investigated in an attempt to develop new
35 therapeutic strategies for this condition. Research is also needed into optimum timing of treatment
36 after CRVO. The cost-effectiveness of diagnostic technologies for determining when retreatment is
37 necessary should be examined.
38
39
40
41
42

43
44 We also need better treatments since a significant proportion of patients do not improve with all of
45 these drugs
46
47

48
49 Future RCTs should include longer term outcomes, as functional results observed at six months or
50 even one year may not necessarily be representative of what is likely to be achieved longer term
51 and, furthermore, potential side effects of treatments, such as retinal atrophy after repeated
52 injections of anti-VEGFs, may not be captured in shorter term studies.
53
54
55
56
57
58
59
60

Conclusions

Bevacizumab, ranibizumab, aflibercept and triamcinolone appear to be effective in improving the number of patients who gain 15 letters or more in CRVO. There are mixed results for dexamethasone and pegaptanib. Steroids were associated with cataract progression and increased IOP. Long-term data on effectiveness and safety are needed. Head-to-head trials and research to identify “responders” is needed to help clinicians make the right choices for their patients.

For peer review only

1
2
3 **Acknowledgments:** None
4

5 **Conflict of interest:** None
6

7 **Funding:** This research received no specific grant from any funding agency in the public, commercial
8 or not-for-profit sectors
9

10
11 **Contributions:** NW devised the idea for the review. JF wrote the protocol and all authors
12 contributed to the design of the protocol. RC undertook the literature searches. JF, CC and ST
13 screened titles and abstracts. CC, ST and DS extracted the data. All authors contributed to the
14 interpretation of the results. JF, NL, RC, CC and SB contributed to the first draft of the article. All
15 authors reviewed and commented on the final manuscript.
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1: PRISMA statement

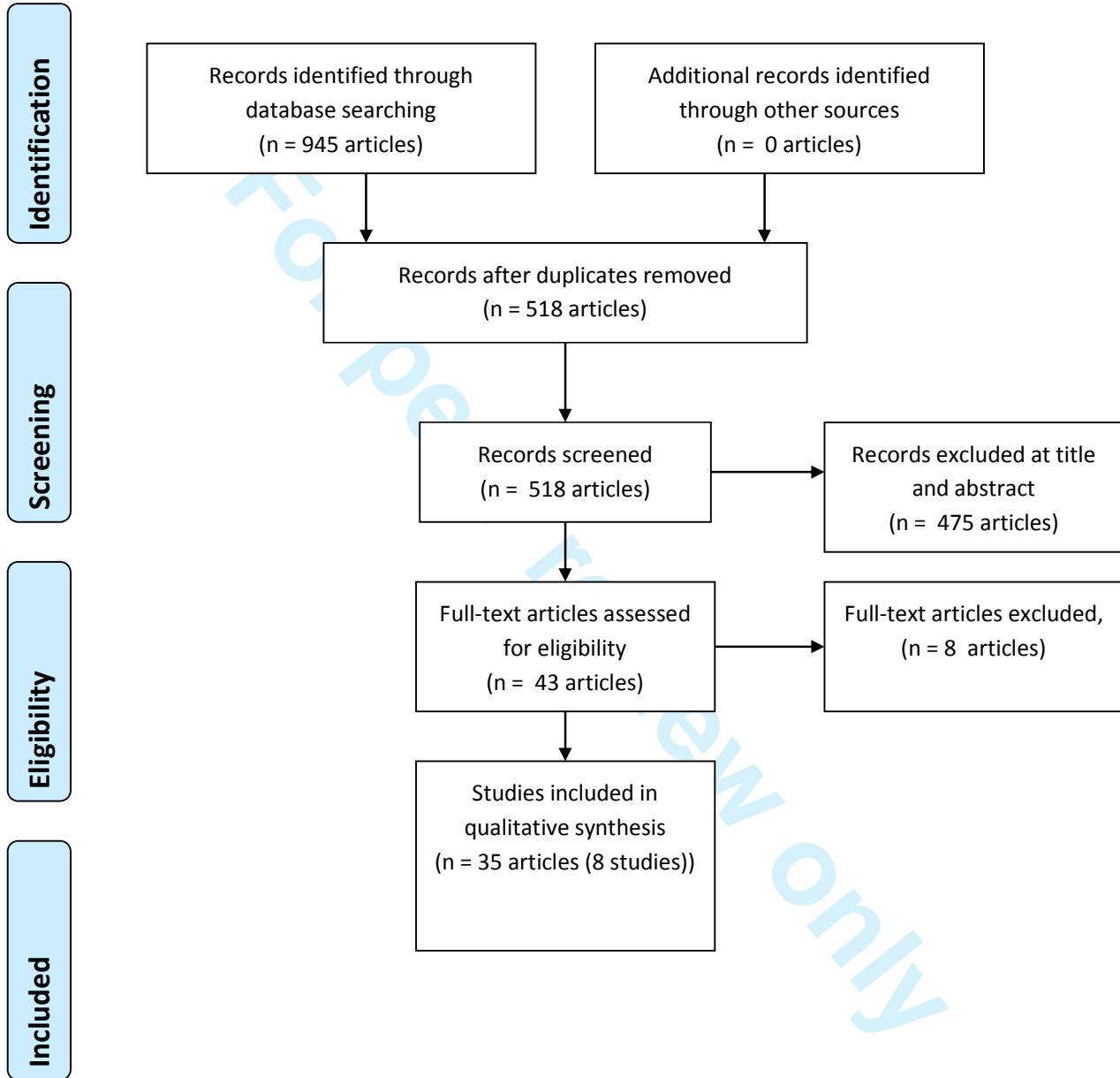
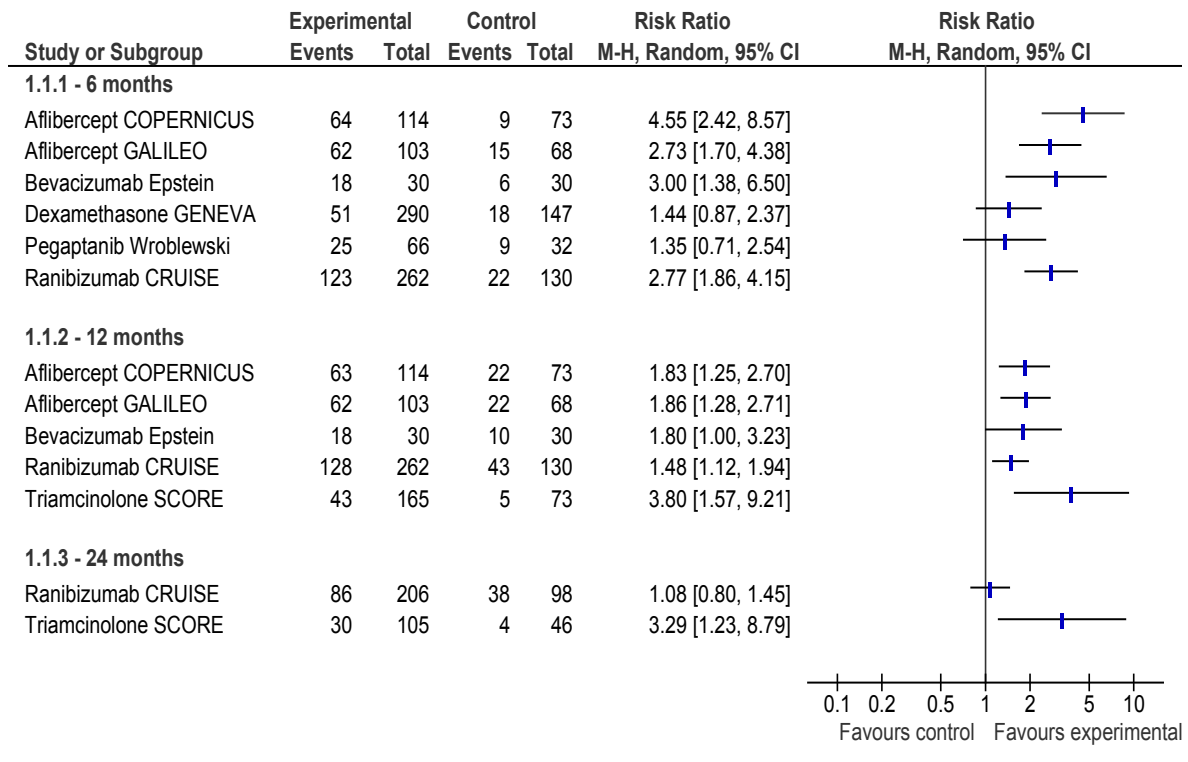


Figure 2. Study results for the primary outcome (≥ 15 ETDRS letter gain).



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Table 1: Study characteristics

Study	Participants and baseline values	Intervention / Outcomes
DEXAMETHASONE		
<p>GENEVA 2010 ff. ^{11;17;18}</p> <p>International</p> <p>Setting: multicentre (167 centres in 24 countries, so a mean of 2.6 patients per centre)</p> <p>Study aim: to evaluate the effects of dexamethasone intravitreal implant in patients with macular oedema secondary to CRVO or BRVO (only data for CRVO reported here)</p> <p>Design: 2 identical double-blind, sham-controlled RCTs, phase 3</p> <p>Follow-up: primary endpoint for the masked trial: 6 months; primary endpoint for the open-label extension: 12 months</p> <p>Overall quality: 5.5/6</p>	<p>N: CRVO – 437 eyes of 437 patients randomised; 94% follow-up at 6 months</p> <p>Inclusion criteria: ≥18 years; reduced VA due to macular oedema due to CRVO or BRVO which in the investigator’s opinion, is unlikely to be adversely affected if not treated for 6 months; duration of macular oedema 6 weeks to 9 months in patients with CRVO; BCVA 34 to 68 ETDRS letters (~20/200 and 20/50 Snellen equivalent) in the study eye and >34 letters in the non-study eye; CRT ≥300 µm (OCT)</p> <p>Exclusion criteria: <i>study eye:</i> clinically significant epiretinal membrane; use of periocular corticosteroid within 6 months or topical nonsteroidal anti-inflammatory drug or corticosteroid within 1 month; intraocular surgery or laser within 30 days of study or anticipated; history of intravitreal use of corticosteroid or any other drug; glaucoma; IOP >23 mmHg if untreated or >21 if treated with one medication; treatment with ≥2 IOP-lowering medications; active retinal, optic disc or choroidal neovascularisation; history of herpetic infection; rubeosis iridis, aphakia or anterior-chamber intraocular lens; any ocular condition that would prevent a 15-letter VA improvement; preretinal or vitreous haemorrhage, lens opacity, media opacity that would preclude clinical or photographic evaluation; history of pars plana vitrectomy; <i>any eye:</i></p>	<p>DEX 0.7 (n=136): sustained delivery, biodegradable dexamethasone intravitreal implant (Ozurdex), 0.7 mg implant inserted into the vitreous cavity through the pars plana using a customised, single-use, 22-gauge applicator</p> <p>DEX 0.35 (n=154): DEX 0.35 mg implant inserted following the same method</p> <p>Sham (n=147): a needleless applicator was placed against the conjunctiva to simulate the placement of study medication.</p> <p>Regimen for all groups: before inserting the implant, the study eye was anaesthetised with topical and subconjunctival anaesthetics and prepared according to standard clinical practice for eyes undergoing intravitreal injection; patients were treated with a topical ophthalmic antibiotic 4 times daily starting 3 days before the day of their study procedure (day 0) and continuing for 3 days after the procedure</p> <p>Extension: patients completing 180 days were eligible to enter a 6 month open label extension where they received DEX 0.7 mg implant</p> <p>Primary end point: gain of ≥15 ETDRS letters; for the open-label extension: safety</p>

Study	Participants and baseline values	Intervention / Outcomes
	<p>active ocular infection; history of steroid-induced IOP–increase; diabetic retinopathy; <i>other</i>: uncontrolled systemic disease; current or anticipated use of systemic steroids or anticoagulants</p> <p>Age (years): 62.7 to 65.2 years</p> <p>Sex: 43.7 to 49.2% (CRVO and BRVO together)</p> <p>Baseline VA (ETDRS letters):52.4 SD10.6</p> <p>Baseline CRT (µm):DEX 0.7: 648; Sham: 620</p> <p>Other ocular information: phakic status (%): 85 to 88%</p> <p>Duration of macular oedema: mean 4.8 to 4.9 months;<90 days: 14.3 to 15.4%; >90 to <180 days: 54.4 to 57.4%, >180 days: 27.1 to 31.3%</p> <p>Comorbidities: diabetes mellitus 14 to 15%, hypertension 62 to 64%, coronary artery disease 9 to 13%, IOP-lowering medication at baseline 4 to 6% (all for CRVO and BRVO together)</p>	<p>Other outcomes: proportion of eyes achieving at least a 10 and 15 letter improvement from baseline; the proportion of eye exhibiting ≥15 letters of worsening; BCVA; subgroup analysis according to RVO diagnosis (BRVO and CRVO) and duration of macular oedema at baseline; CRT and safety</p> <p>Outcome assessment: evaluation at 1, 7, 30, 60, 90 and 180 days after study treatment for both parts of the study</p>
TRIAMCINOLONE		
<p>SCORE 2009 ff.¹⁹⁻³²</p> <p>USA</p> <p>Setting: multicentre</p> <p>Study aim: to compare the effects of 1 and 4 mg preservative-free</p>	<p>N: 271 eyes of 271 patients randomised; 83% (observation) and 90% (intervention) completed 12 months</p> <p>Inclusion criteria: centre-involved macular oedema secondary to CRVO, BCVA 19 to 73 ETDRS letters (Snellen equivalent ~20/400 to 20/40), CRT >250 µm by OCT; media clarity, papillary dilatation and participant</p>	<p>Tria (1 mg) (n=92): 1 mg (0.05 ml) of preservative-free, nondispersible formulation of triamcinolone (average number of injections 2.2 at 12 months)</p> <p>Tria (4 mg) (n=91): 4 mg (0.05 ml) of preservative-free, nondispersible formulation of triamcinolone(average number of injections 2.0 at 12 months)</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Participants and baseline values	Intervention / Outcomes
<p>intravitreal triamcinolone with observation in eyes with vision loss associated with macular oedema secondary to perfused CRVO</p> <p>Design: RCT</p> <p>Follow-up: primary end point 12 months, FU planned up to 36 months</p> <p>Overall quality: 3/6</p>	<p>cooperation sufficient for adequate fundus photographs</p> <p>Exclusion criteria: macular oedema due to causes other than CRVO, ocular condition such that visual acuity would not improve from resolution of oedema, substantial cataract, prior treatment with intravitreal corticosteroids or peribulbar steroid injection within 6 months, photocoagulation (prior 4 months or anticipated), prior pars plana vitrectomy, major ocular surgery (prior 6 months or anticipated), IOP \geq25 mmHg, open-angle glaucoma, steroid-induced IOP-elevation requiring IOP-lowering treatment, pseudoexfoliation, aphakia</p> <p>Age: 68.0 SD 12.4 years</p> <p>Sex: 45% female</p> <p>Duration of macular oedema: 4.3 SD3.7 months</p> <p>Baseline VA (ETDRS letters): 51.2 SD14.1</p> <p>Baseline CRT (μm): 659 SD229</p> <p>Other ocular information: 81% phakic, IOP 15.5 SD3.2 mmHg</p> <p>Comorbidities: 23% diabetes mellitus, 73% hypertension, 21% coronary artery disease, 21% history of cancer</p>	<p>The form of triamcinolone used was Trivaris, no longer available. It was made by the manufacturer of Ozurdex (Allergan)</p> <p>Obs (n=88): observation</p> <p>Regimen for all groups: all intervention eyes received standardised ocular surface preparation prior to injection (eyelid speculum, topical anaesthetic, topical antibiotics, asepsis with povidone iodine); retreatment every 4 months unless (1) treatment was deemed successful (defined), (2) treatment was contraindicated because of significant adverse effect, (3) additional treatment was considered 'apparently futile' (defined)</p> <p>Primary end point: gain of \geq15 ETDRS letters</p> <p>Other outcomes: BCVA, intraocular pressure, eye examination including dilated fundus examination, OCT scan for thickness, , lens opacities, , adverse events</p> <p>Outcome assessment: follow-up visits every 4 months for 36 months</p>
<p>ROVO 2013³³</p>	<p>N: 90 patients randomised; 82% evaluated</p> <p>Inclusion criteria: history of CRVO not longer than 12</p>	<p>Tria (n=25): single intravitreal injection of 4 mg triamcinolone acetonide (100 μl) applied after povidone</p>

Study	Participants and baseline values	Intervention / Outcomes
<p>Austria</p> <p>Setting: multicentre (7 centres in 7 countries)</p> <p>Study aim: to compare the effects of radial optical neurotomy with intravenous triamcinolone and natural history (placebo) in patients with CRVO</p> <p>Design: RCT, placebo-controlled</p> <p>Follow-up: primary end point 12 months</p> <p>Overall quality: 3.5/6</p>	<p>months; VA of ≥ 0.3 logMAR (≤ 85 letters) (for perfused CRVO: VA > 1 logMAR (> 50 letters) or no VA improvement over 4 weeks)</p> <p>Exclusion criteria: dense cataract, severe ophthalmologic conditions (severe retinopathy, presence of advanced optic atrophy, uncontrolled glaucoma), pregnancy, allergy against fluoresceine or indocyanine green, any handicap which could prevent patients from attending follow-up visits</p> <p>Age: not reported</p> <p>Sex: 36% female</p> <p>Duration of macular oedema: not reported</p> <p>Baseline VA (ETDRS letters) : 1.07 logMAR (interquartile range 0.78 to 1.7) (~46 letters)</p> <p>Baseline CRT (μm): 569 to 657 μm</p> <p>Other ocular information: not reported</p> <p>Comorbidities: 23% diabetes mellitus, 49% hypertension, 17% cardiovascular disease, 4% hypercoagulopathies, 1% leukaemia, 2% anaemia</p>	<p>iodine drops; postoperative topical antibiotics</p> <p>RON (n=38): radial optical neurotomy under general anaesthesia (detailed procedure described)</p> <p>Pla (n=20): eyes prepared as for triamcinolone injection but sham injection performed (empty syringe without needle pressed against the eye)</p> <p>Primary end point: gain of ≥ 15 ETDRS letters</p> <p>Other outcomes: BCVA, CRT, safety</p> <p>Outcome assessment: 12 months</p>
AFLIBERCEPT		
<p>COPERNICUS 2012^{34;35}</p> <p>International</p>	<p>N: 189 eyes of 189 patients randomised; 95.7% (aflibercept) and 81.1% (sham) completed 24 weeks; 93% (aflibercept) and 77% (sham) completed 52 weeks</p>	<p>VTE (n=114): intravitreal injections of 2 mg aflibercept (50 μl) every 4 weeks for 24 weeks</p> <p>Sham (n=73): sham procedure (empty syringe without</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Participants and baseline values	Intervention / Outcomes
<p>Setting: multicentre, 70 sites in North and South America, India and Israel. Mean 2.7 patients per centre.</p> <p>Study aim: to evaluate the effects of intravitreal aflibercept in patients with macular oedema secondary to CRVO</p> <p>Design: double-blind, sham-controlled RCT, phase 3</p> <p>Follow-up: primary end point 24 weeks, FU 2 years</p> <p>Overall quality: 5/6</p>	<p>Inclusion criteria: adult patients with centre-involved CRVO for a maximum of 9 months, CRT $\geq 250 \mu\text{m}$ with OCT, ETDRS BCVA of 73 to 24 letters (Snellen equivalent 20/40 to 20/320)</p> <p>Exclusion criteria: history of vitreoretinal surgery (incl. radial optic neurotomy or sheathotomy); current bilateral retinal vein occlusion; previous pan-retinal or macular laser photocoagulation; other reasons for decreased visual acuity; ocular conditions with poorer prognosis in the fellow eye; history or presence of age-related macular degeneration, diabetic macular oedema, or diabetic retinopathy; any use of intraocular or periocular corticosteroids or antiangiogenic treatment in the study eye at any time or in the fellow eye in the preceding 3 months; iris neovascularisation, vitreous haemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula; vitreomacular traction or epiretinal membrane significantly affecting central vision; ocular inflammation; uveitis; any intraocular surgery in the preceding 3 months; aphakia; uncontrolled glaucoma, hypertension, or diabetes; spherical equivalent of a refractive error of more than -8 diopters; myopia; infectious blepharitis, keratitis, scleritis, or conjunctivitis; cerebral vascular accident or myocardial infarction in the preceding 6 months; and other conditions that could interfere with interpretation of the results or increase the risk of complications; cataract surgery was not allowed during the 3 months before randomisation.</p>	<p>needle pressed to conjunctival surface) every 4 weeks for 24 weeks</p> <p>Regimen for all groups: all patients eligible to receive pan-retinal photocoagulation for neovascularisation at any time at the discretion of the investigator; patients were not allowed to use other systemic or local medications for treating CRVO in the study eye over the first 52 weeks of the study; a noninvestigational therapy could be used to treat CRVO in the fellow eye</p> <p>Extension: during weeks 24 to 52, patients in both groups were evaluated monthly and received aflibercept if they met protocol-specified retreatment criteria, and received a sham injection if retreatment was not indicated (3.9 SE0.3 injections in the sham group and 2.7 SE0.2 injections in the VTE group); after the first year, patients continued in a 1 year extension phase with as needed dosing</p> <p>Primary end point: gain of ≥ 15 ETDRS letters</p> <p>Other outcomes: BCVA, CRT, proportion of patients progressing to neovascularisation of the anterior segment, optic disc or elsewhere in the retina, changes in vision-related quality of life (National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), safety</p> <p>Outcome assessment: examination every 4 weeks up to 24 weeks, 52 weeks</p>

Study	Participants and baseline values	Intervention / Outcomes
	<p>Age: 66.3 SD 13.9 years</p> <p>Sex: 43% female</p> <p>Time since CRVO diagnosis: 2.4 SD2.8 months; 62.0% ≤2 months, 37.4% >2 months</p> <p>Baseline VA (ETDRS letters) : 50.0 SD14.1 ; 75.4% >20/200</p> <p>Baseline CRT (µm): 665.8 SD239.8</p> <p>Other ocular information: 67.9% perfused retinal occlusion, IOP 15.1 SD3.08 mmHg</p> <p>Comorbidities: not reported</p>	
<p>GALILEO 2012^{36,37}</p> <p>International</p> <p>Setting: multicentre, 10 countries in Europe and Asia; 63 centres in total</p> <p>Study aim: to evaluate the effects of intravitreal aflibercept in patients with macular oedema secondary to CRVO</p> <p>Design: double-blind, sham-controlled RCT, phase 3</p> <p>Follow-up: primary end point 24 weeks, FU up to 12 months, planned</p>	<p>N: 177 eyes of 177 patients randomised; 90.6% (aflibercept) and 78.9% (sham) completed 24 weeks</p> <p>Inclusion criteria: treatment-naïve patients, age ≥18 years, centre-involved CRVO for a maximum of 9 months, CRT ≥250 µm with OCT, ETDRS BCVA of 73 to 24 letters (Snellen equivalent 20/40 to 20/320)</p> <p>Exclusion criteria: uncontrolled glaucoma (IOP≥25 mmHg), filtration surgery, bilateral manifestation of retinal vein occlusion, iris neovascularisation, previous treatment with anti-VEGF agents, pan-retinal or macular laser photocoagulation, intraocular corticosteroids, pregnant</p> <p>Age: 61.5 SD 12.9 years</p>	<p>VTE (n=103): intravitreal injections of 2 mg aflibercept every 4 weeks for 24 weeks</p> <p>Sham (n=71): sham procedure (empty syringe without needle pressed to conjunctival surface) every 4 weeks for 24 weeks</p> <p>Regimen for all groups: pan-retinal photocoagulation allowed at any time for all patients if they progressed to neovascularisation of the anterior segment, optic disc or fundus</p> <p>Extension: during weeks 24 to 52, patients remained in their original treatment groups but received their allocated treatment as needed; beginning from week 52 to week 76 both groups received treatment every 8</p>

Study	Participants and baseline values	Intervention / Outcomes
<p>up to 76 weeks</p> <p>Overall quality: 4/6</p>	<p>Sex: 44.4% female</p> <p>Time since CRVO diagnosis: 81.8 SD85.4 days; 52.6% <2 months, 46.2% ≥2 months, 1.2% missing</p> <p>Baseline VA (ETDRS letters) : 52.2 SD15.7, 83% >20/200</p> <p>Baseline CRT (μm): 665.5 SD231.0</p> <p>Other ocular information: 83.6% perfused retinal occlusion, IOP 14.9 SD2.7 mmHg</p> <p>Comorbidities: Renal impairment: 31% mild, 8.2% moderate, 1.2% severe; 2.9% hepatic impairment</p>	<p>weeks</p> <p>Primary end point: gain of ≥15 ETDRS letters</p> <p>Other outcomes: BCVA, CRT, proportion of patients progressing to neovascularisation of the anterior segment, optic disc or elsewhere in the fundus, changes in vision-related and overall quality of life (National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), European Quality of Life-5 Dimensions (EQ-5D)), safety</p> <p>Outcome assessment: 24 weeks, 52 weeks</p>
PEGAPTANIB		
<p>Wroblewski 2009³⁸⁻⁴⁴</p> <p>International</p> <p>Number of sites: not reported</p> <p>Setting: multicentre, practitioners' offices and clinics in Australia, France, Germany, Israel, Spain, USA</p> <p>Study aim: to evaluate the effects of intravitreal pegaptanib sodium in patients with macular oedema secondary to CRVO</p> <p>Design: double-blind, sham-</p>	<p>N: 98 eyes of 98 patients randomised; 93% completed 30 weeks</p> <p>Inclusion criteria: age ≥18 years, CRVO with onset within 6 months prior to baseline, CRT ≥250 μm with OCT, ETDRS BCVA of 65 to 20 letters (Snellen equivalent 20/50 to 20/400) and better than 35 letters (20/200) in the fellow eye</p> <p>Exclusion criteria: subtenon corticosteroid administration for any ophthalmic condition; prior panretinal or sector scatter photocoagulation; signs of old branch retinal vein occlusion or CRVO in the study eye; any other retinal vascular disease including diabetic retinopathy; eyes with a brisk afferent pupillary defect;</p>	<p>PS 0.3 mg (n=33): intravitreal injections of 0.3 mg pegaptanib sodium every 6 weeks for 24 weeks (5 injections)</p> <p>PS 1 mg (n=33): intravitreal injections of 1 mg pegaptanib sodium every 6 weeks for 24 weeks (5 injections)</p> <p>Sham (n=32): sham procedure (blunt pressure applied to the globe without a needle) every 6 weeks for 24 weeks</p> <p>Regimen for all groups: antiseptis procedures were the same for all participants (including those receiving sham); all participants received injected subconjunctival anaesthetic; panretinal photocoagulation permitted at</p>

Study	Participants and baseline values	Intervention / Outcomes
<p>controlled RCT, phase 2</p> <p>Follow-up: primary end point 30 weeks, FU up to 12 months</p> <p>Overall quality: 6/6</p>	<p>vitreous haemorrhage except for breakthrough haemorrhage from intraretinal haemorrhage; evidence of any neovascularisation involving the iris, disc, or retina; any other clinically significant concomitant ocular diseases</p> <p>Age: 59 to 64 years</p> <p>Sex: 47% female</p> <p>Time from occlusive event to study entry: 77 to 82 days</p> <p>Baseline VA (ETDRS letters): 47.6 to 48.5 letters</p> <p>Baseline CRT (μm): 632 to 688</p> <p>Other ocular information: not reported</p> <p>Comorbidities: not reported</p>	<p>any time point for neovascularisation according to the Central Vein Occlusion Study protocol; intravitreal steroids not permitted at any time</p> <p>Extension: FU to 52 weeks</p> <p>Primary end point: gain of ≥ 15 ETDRS letters</p> <p>Other outcomes: BCVA, loss of ≥ 15 letters, CRT, proportion of eyes progressing to retinal or iris neovascularisation, safety</p> <p>Outcome assessment: assessments every 6 weeks up to week 30, FU to week 52</p>
RANIBIZUMAB		
<p>CRUISE 2010 ff.^{10,45,46}</p> <p>USA</p> <p>Number of sites: not reported</p> <p>Setting: multicentre</p> <p>Study aim: to evaluate the effects of intravitreal ranibizumab (0.3 or 0.5 mg) in patients with macular oedema secondary to CRVO</p>	<p>N: 392 eyes of 392 patients randomised; 97.7% (ran 0.3 mg), 91.5% (ran 0.5 mg), and 88.5% (sham) completed 6 months</p> <p>Inclusion criteria: age ≥ 18 years, foveal centre-involved macular oedema secondary to CRVO diagnosed within 12 months before study began, CRT $\geq 250 \mu\text{m}$ with OCT, BCVA 20/40 to 20/320 (ETDRS charts)</p> <p>Exclusion criteria: prior episode of retinal vein</p>	<p>Ran 0.3 mg (n=132): intravitreal injections of 0.3 mg ranibizumab monthly for 6 months (maximum 6 injections)</p> <p>Ran 0.5 mg (n=130): intravitreal injections of 0.5 mg ranibizumab monthly for 6 months (maximum 6 injections)</p> <p>Sham (n=130): sham procedure (empty syringe without needle pressed to the injection site) monthly for 6 months</p>

Study	Participants and baseline values	Intervention / Outcomes
<p>Design: double-blind, sham-controlled RCT, phase 3</p> <p>Follow-up: primary end point 6 months, FU up to 12 months</p> <p>Overall quality: 4.5/6</p>	<p>occlusion, brisk afferent pupillary defect, >10-letter improvement in BCVA between screening and day 0, history of radial optic neurotomy or sheathotomy, intraocular corticosteroid use in study eye in prior 3 months, history or presence of wet or dry age-related macular oedema, recent or anticipated panretinal scatter photocoagulation or sector laser photocoagulation, laser photocoagulation for macular oedema in prior 4 months, evidence on examination of any diabetic retinopathy, stroke or myocardial infarction in prior 3 months, prior anti-VEGF treatment in study or fellow eye in prior 3 months or systemic anti-VEGF or pro-VEGF treatment in prior 6 months</p> <p>Age: 65.4 SD13.1 to 69.7 SD11.6 years</p> <p>Sex: 38.5 to 46.2% female</p> <p>Time since CRVO diagnosis: 2.9 SD2.9 to 3.6 SD3.2 months; 65.9 to 72.3% ≤3 months</p> <p>Baseline VA (ETDRS letters): 47.4 to 49.2 (SD 14.6 to 14.8) (range 9 to 72), 38.5 to 42.3% ≥55</p> <p>Baseline CRT (µm): 679.9 SD242.4 to 688.7 SD253.1</p> <p>Other ocular information: IOP 14.9 SD3.3 to 15.1 SD3.1 mmHg, 10.0 to 16.9% IOP-lowering medication, n=2 >10 disc areas of non-perfusion; fellow eye BCVA 78.8 SD 17.4 to 80.0 SD12.5</p>	<p>Regimen for all groups: prior to injection or sham: topical anaesthetic drops, subconjunctival injection of 2% lidocaine, cleaning of injection site with 5% povidone iodine</p> <p>Extension: months 6 to 12: all patients could receive intraocular ranibizumab (previously assigned dose or 0.5 mg for the sham group) if they met pre-specified functional and anatomic criteria (3.7 injections sham group, 3.8 injections 0.3 mg ran group, 3.3 injections 0.5 mg ran group); after 12 months' FU, 304 CRUISE patients continued in the HORIZON study for another 12 months, where patients were evaluated at least every 3 months and were eligible to receive an intravitreal injection of 0.5 mg ranibizumab if they fulfilled prespecified criteria (2.9 SD2.7 injections sham group, 3.8 SD2.8 injections 0.3 mg ran group, 3.5 SD2.7 injections 0.5 mg ran group)</p> <p>Primary end point: mean change from baseline BCVA</p> <p>Other outcomes: percentage gaining ≥15 letters, percentage losing ≥15 letters, CRT, percentage with CRT <250 µm, vision-related quality of life (National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), safety</p> <p>Outcome assessment: monthly visits up to 12 months; 3-monthly evaluation up to 24 months (HORIZON)</p>

Study	Participants and baseline values	Intervention / Outcomes
	Comorbidities: not reported	
BEVACIZUMAB		
<p data-bbox="174 430 367 462">Epstein 2012⁴⁷⁻⁴⁹</p> <p data-bbox="174 487 268 519">Sweden</p> <p data-bbox="174 609 567 673">Setting: Single centre; St. Eriks Eye Hospital Stockholm</p> <p data-bbox="174 698 598 828">Study aim: to evaluate the effects of intraocular injections of bevacizumab in patients with macular oedema secondary to CRVO</p> <p data-bbox="174 852 567 917">Design: sham-injection controlled, double masked RCT</p> <p data-bbox="174 950 577 1047">Follow-up: primary end-point 6 months; open label extension up to 12 months</p> <p data-bbox="174 1071 399 1104">Overall quality: 5/6</p>	<p data-bbox="621 430 1228 495">N: 60 eyes of 60 patients randomised; 93% completed open label extension</p> <p data-bbox="621 576 1218 673">Inclusion criteria: CRVO of ≤ 6 months; BCVA 15 to 65 ETDRS letters (Snellen equivalent $\sim 20/50$ to $20/500$), CRT $\geq 300 \mu\text{m}$ by OCT</p> <p data-bbox="621 706 1249 933">Exclusion criteria: CRVO with neovascularisation; previous treatment for CRVO; intraocular surgery during previous 3 months; vascular retinopathy of other causes; glaucoma with advanced visual field defect or uncontrolled ocular hypertension $>25 \text{ mmHg}$ despite full therapy; myocardial infarction or stroke during last 12 months</p> <p data-bbox="621 1023 892 1055">Age: 70.5 SD 12.6 years</p> <p data-bbox="621 1079 808 1112">Sex: 40% female</p> <p data-bbox="621 1136 1207 1201">Time from diagnosis to inclusion: 8.8 SD 5.7 weeks; 71.7% <90 days, 28.3% >90 days</p> <p data-bbox="621 1226 1239 1291">Baseline VA (ETDRS letters) : 44.1 SD 15.5 ; 31.7% <34, 68.3% >34</p>	<p data-bbox="1276 430 1858 495">Bev (n=30): 1.25 mg (0.05 ml) bevacizumab via pars plana</p> <p data-bbox="1276 519 1879 584">Sham (n=30): sham injection (syringe without needle pressed to the globe)</p> <p data-bbox="1276 609 1900 738">Regimen for all groups: 4 injections received, one every 6 weeks; eyes treated with topical antibiotics 30 min before injection, topical chlorhexidine, topical anaesthesia with 1% tetracaine</p> <p data-bbox="1276 771 1900 868">Open label extension: months 6 to 12, intravitreal bevacizumab injections every 6 weeks (4 injections) for all patients</p> <p data-bbox="1276 950 1774 982">Primary end point: gain of ≥ 15 ETDRS letters</p> <p data-bbox="1276 1006 1890 1144">Other outcomes: BCVA, OCT images, CRT, fluorescein angiogram, colour and red-free photography, slit-lamp examination with dilated fundus-examination, intraocular pressure, adverse events</p> <p data-bbox="1276 1169 1900 1234">Outcome assessment: follow-up visits every 6 weeks up to 24 weeks</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Participants and baseline values	Intervention / Outcomes
	<p>Baseline CRT (μm): 721 SD 269</p> <p>Comorbidities: 48.3% hypertension, 6.7% diabetes mellitus</p>	

Abbreviations: BCVA – best corrected visual acuity, CRT – central retinal thickness, CRVO – central retinal vein occlusion, ETDRS – Early Treatment Diabetic Retinopathy Study, FU – follow-up, IOP – intraocular pressure, OCT – optical coherence tomography, SD – standard deviation, SE – standard error

For peer review only

Table 2: Study results and adverse events

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events
DEXAMETHASONE		

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events					
GENEVA 2010 ff. ^{11;17;18}		Baseline	6 months	p	12 months	p	AE	DEX 0.35	DEX 0.7 (n = 133)	Sham (n = 147)	p
	BCVA (mean letters)						6 months				
	<i>DEX 0.35</i>	-	-				Overall incidence of ocular adverse events				
	<i>DEX 0.7</i>	52.4 SD 10.6	+0.1	< 0.001 vs sham	<i>DEX 0.7/0.7</i>	+2 (estimated from graph)		68.4%	49.7%		
	<i>Sham</i>	53.3 SD 10.8	-1.8		<i>Sham/DEX 0.7</i>	-1.4 (ditto)	Common Ocular Adverse Events				
	≥15 letters gained						Intraocular pressures increased	40 (30.1%)	2 (1.4%)	<0.001	
	<i>DEX 0.35</i>		17%	NS vs sham			Common treatment-related Ocular Adverse Events				
	<i>DEX 0.7</i>		18.4%	NS vs sham	<i>DEX 0.7/0.7, day 240</i>	27%	IOP increased	39 (29.3%)	1 (0.7%)	<0.001	
					<i>DEX 0.7 (n=19), day 360</i>	26%	Cataract adverse events				
	<i>Sham</i>		12.2%	NS vs sham	<i>Sham/DEX 0.7, day 240</i>	21%	Cataract	3 (2.3%)	2 (1.4%)		
	≥15 letters lost						Cataract subcapsular	4 (3.0%)	1 (0.7%)		
	<i>DEX 0.35</i>		-	-			Cataract nuclear	3 (2.3%)	1 (0.7%)		
	<i>DEX 0.7</i>		14.0%	NS			Cataract cortical	1 (0.8%)	3 (2.0%)		
	<i>Sham</i>		20.4%				Serious adverse events – not given separately for CRVO				
	Subgroups										
Duration of macular oedema											
>90 days	<i>DEX 0.7</i>	17.7%									
	<i>Sham</i>	9.6%									
≤90 days	<i>DEX 0.7</i>	26.0%									
	<i>Sham</i>	27.3%									

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events																																								
	<p>CRT (μm):</p> <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>6months (mean)</th> <th>p</th> <th>12 months (mean)</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>CRT</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>DEX 0.35</td> <td>-</td> <td>-</td> <td></td> <td></td> <td></td> </tr> <tr> <td>DEX 0.7</td> <td>647.6</td> <td>-118.2</td> <td>NS vs sham</td> <td></td> <td></td> </tr> <tr> <td>Sham</td> <td>619.8</td> <td>-125.3</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>		Baseline	6months (mean)	p	12 months (mean)	p	CRT						DEX 0.35	-	-				DEX 0.7	647.6	-118.2	NS vs sham			Sham	619.8	-125.3														
	Baseline	6months (mean)	p	12 months (mean)	p																																					
CRT																																										
DEX 0.35	-	-																																								
DEX 0.7	647.6	-118.2	NS vs sham																																							
Sham	619.8	-125.3																																								
TRIAMCINOLONE																																										
<p>SCORE 2009 ff.¹⁹⁻³²</p> <p>1 mg intravitreal triamcinolone (2.2 injections over 12 months) (n=92)</p> <p>versus 4 mg intravitreal triamcinolone (2</p>	<p>BCVA (ETDRS letters):</p> <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>12 months</th> <th>p</th> <th>24 months</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>BCVA (letters, 95% CI)</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Tria 1 mg</td> <td>50.6 SD 14.9</td> <td>-1.2 (-6.4 to +4.1)</td> <td><0.05 vs obs</td> <td>-4.4 (-11.5 to +2.8)</td> <td>NR</td> </tr> <tr> <td>Tria 4 mg</td> <td>51.0 SD 14.4</td> <td>-1.2 (-6.3 to +4.0)</td> <td><0.05 vs obs</td> <td>-2.4 (-9.3 to +4.4)</td> <td></td> </tr> </tbody> </table>		Baseline	12 months	p	24 months	p	BCVA (letters, 95% CI)						Tria 1 mg	50.6 SD 14.9	-1.2 (-6.4 to +4.1)	<0.05 vs obs	-4.4 (-11.5 to +2.8)	NR	Tria 4 mg	51.0 SD 14.4	-1.2 (-6.3 to +4.0)	<0.05 vs obs	-2.4 (-9.3 to +4.4)		<p>Ocular Adverse Events</p> <table border="1"> <thead> <tr> <th>AE</th> <th>Tria 1 mg</th> <th>Tria 4 mg</th> <th>Obs</th> </tr> </thead> <tbody> <tr> <td>12 months</td> <td></td> <td></td> <td></td> </tr> <tr> <td><i>Elevated IOP or glaucoma</i></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Initiation of IOP-lowering medication</td> <td>20%</td> <td>35%</td> <td>8%</td> </tr> </tbody> </table>	AE	Tria 1 mg	Tria 4 mg	Obs	12 months				<i>Elevated IOP or glaucoma</i>				Initiation of IOP-lowering medication	20%	35%	8%
	Baseline	12 months	p	24 months	p																																					
BCVA (letters, 95% CI)																																										
Tria 1 mg	50.6 SD 14.9	-1.2 (-6.4 to +4.1)	<0.05 vs obs	-4.4 (-11.5 to +2.8)	NR																																					
Tria 4 mg	51.0 SD 14.4	-1.2 (-6.3 to +4.0)	<0.05 vs obs	-2.4 (-9.3 to +4.4)																																						
AE	Tria 1 mg	Tria 4 mg	Obs																																							
12 months																																										
<i>Elevated IOP or glaucoma</i>																																										
Initiation of IOP-lowering medication	20%	35%	8%																																							

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events				
injections over 12 months (n=91) versus observation (n=88)	Obs	52.1 SD 13.1	-12.1 (-17.1 to -7.1)		-10.7 (-17.4 to -4.1)		IOP >35 mm Hg (n)	5	8	1
	≥15 letters gained (95% CI)						IOP >10 mm Hg above baseline (n)	15	24	2
	Tria 1 mg		26.5% (17 to 36)	0.001 vs obs	31% (19 to 43)	NR	Laser peripheral iridotomy (n)	0	1	0
	Tria 4 mg		25.6% (16 to 35)	0.001 vs obs	26% (14 to 38)		Trabeculectomy (n)	0	0	0
	Obs		6.8% (1 to 13)		9% (1 to 17)		Tube shunt (n)	2	0	0
	≥15 letters lost						Cataract			
	Tria 1 mg		25.3%		31%		Lens opacity onset or progression	26%	33%	18%
	Tria 4 mg		25.6%		26%		Cataract surgery (n)	0	4	0
	Obs		43.8%		48%	NS, p=0.06 tria vs obs	<i>At least 1 of the following adverse events (n):</i>	11	6	9
	CRT (μm):						Infectious endophthalmitis (n)	0	0	0
		Baseline	12 months (median, IQR)	p	24 months (median, IQR)	p	Non-infectious endophthalmitis (n)	0	0	0

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events			
	CRT						Retinal detachment (n)	0	0	0
	Triia 1 mg	643 SD 226	-196 (-390 to -62)	NR	-286 (-458 to -119)	NR	Iris neovascularisation or neovascular glaucoma	9	4	2
	Triia 4 mg	641 SD 248	-261 (-407 to -79)		-236 (-421 to -63)		Retinal neovascularisation (n)	2	2	4
	Obs	695 SD 208	-277 (-418 to -40)		-304 (-465 to -108)		Vitreous hemorrhage (n)	4	0	4
	CRT <250 µm			CRT <250 µm			<i>Other ocular surgical procedures</i>			
	Triia 1 mg		32%	NR	50%	NR	YAG capsulotomy	0	0	1
	Triia 4 mg		45%		39%		Sector or panretinal scatter photocoagulation	9	3	5
	Obs		28%		38%		Pars plana vitrectomy	2	0	1
	Results for subgroups (based on baseline BCVA (73 to 59, 58 to 49, 48 to 19), baseline CRT (<500 µm, ≥500 µm), duration of macular oedema (≤3 months, >3 months, pseudophakic at baseline) were consistent with the overall results (significance levels for comparisons not reported)						Selected Events at 12-24 months			
							<i>Glaucoma procedures</i>			
							Laser peripheral iridotomy	0	0	0

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events																																			
		Trabeculectomy	0	0	0																																
		Tube shunt	0	2	0																																
		<i>Cataract</i>																																			
		Cataract surgery	3	21	0																																
		Reports of systemic adverse events were similar between groups																																			
ROVO 2013³³ 4 mg intravitreal triamcinolone acetonide (single injection) versus radial optical neurotomy versus sham injection	BCVA (logMAR): <table border="1" data-bbox="380 678 1486 1323"> <thead> <tr> <th></th> <th>Baseline</th> <th>12 months</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>BCVA (logMAR, interquartile range)</td> <td></td> <td></td> <td></td> </tr> <tr> <td><i>Tria 4 mg</i></td> <td>1.02 (0.75, 2.0)</td> <td>0.86 (0.51, 1.78) (-0.16)</td> <td>NR</td> </tr> <tr> <td><i>RON</i></td> <td>1.46 (0.84, 2.0)</td> <td>0.75 (46, 1.22) (-0.71)</td> <td></td> </tr> <tr> <td><i>Sham</i></td> <td>1.02 (0.9, 1.36)</td> <td>1.02 (0.85, 3.0) (0)</td> <td></td> </tr> <tr> <td>% with VA improvement</td> <td></td> <td></td> <td></td> </tr> <tr> <td><i>Tria 4 mg</i></td> <td></td> <td>20%</td> <td>0.034 vs RON, NS vs placebo</td> </tr> <tr> <td><i>RON</i></td> <td></td> <td>47%</td> <td></td> </tr> </tbody> </table>		Baseline	12 months	p	BCVA (logMAR, interquartile range)				<i>Tria 4 mg</i>	1.02 (0.75, 2.0)	0.86 (0.51, 1.78) (-0.16)	NR	<i>RON</i>	1.46 (0.84, 2.0)	0.75 (46, 1.22) (-0.71)		<i>Sham</i>	1.02 (0.9, 1.36)	1.02 (0.85, 3.0) (0)		% with VA improvement				<i>Tria 4 mg</i>		20%	0.034 vs RON, NS vs placebo	<i>RON</i>		47%		Ocular Adverse Events, 12 months			
	Baseline	12 months	p																																		
BCVA (logMAR, interquartile range)																																					
<i>Tria 4 mg</i>	1.02 (0.75, 2.0)	0.86 (0.51, 1.78) (-0.16)	NR																																		
<i>RON</i>	1.46 (0.84, 2.0)	0.75 (46, 1.22) (-0.71)																																			
<i>Sham</i>	1.02 (0.9, 1.36)	1.02 (0.85, 3.0) (0)																																			
% with VA improvement																																					
<i>Tria 4 mg</i>		20%	0.034 vs RON, NS vs placebo																																		
<i>RON</i>		47%																																			
		AE	Tria 4 mg	RON	Pla																																
		Retinal detachment		7.9%																																	
		Subretinal haemorrhages		5.3%																																	
		Vitreous haemorrhage		2.6%	10%																																
		Subretinal membrane formation		2.6%																																	
		Retinal tear		2.6%																																	
		IOP increase	32%																																		
		Cataract progression	24%	13%	15%																																
		Neovascular glaucoma	12%	5%	15%																																

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				Adverse events			
	<i>Sham</i>	10%		0.009 vs RON	Rubeosis iridis 15%			
	% with VA deterioration				No cases of phthisis, enucleation, endophthalmitis, injury of central vessels, injury of optic nerve			
	<i>Tria 4 mg</i>	NR						
	<i>RON</i>	8%						
	<i>Sham</i>	35%		0.007 vs RON				
	CRT (µm):							
		Baseline	12 months					p
	CRT							
	<i>Tria 4 mg</i>	657	-235					NS
	<i>RON</i>	569	-263					NS
<i>Sham</i>	615	-206						
AFLIBERCEPT								
COPERNICUS 2012 ^{34;35} 2 mg intravitreal aflibercept(every 4 weeks over 24	BCVA (ETDRS letters):				Adverse Events			
		Baseline	24 weeks	p	52 weeks (all VTE PRN)	p		
	BCVA (letters)				AE (24 weeks) VTE Sham			
					Discontinued treatment before week 24 because of AE 0 4.1%			
				At least one AE 83.3% 85.1%				

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events			
weeks)(n=114) versus sham injection (n=73)	VTE	50.7 SD 13.9	+17.3	<0.001	+16.2	<0.001	Ocular AEs	68.4%	68.9%	
	Sham	48.9 SD 14.4	-4.0		+3.8		Patients with at least one serious adverse event	3.5%	13.5%	
extension up to 52 weeks with afibercept PRN in both groups	≥15 letters gained						Vitreous haemorrhage	0	5.4%	
	VTE		56.1%	<0.001	55.3%	<0.001	Neovascular glaucoma	0	2.7%	
	Sham		12.3%		30.1%		Iris neovascularisation	0	2.7%	
	≥10 letters lost						Retinal haemorrhage	0	2.7%	
	VTE		1.8%	NR			Visual acuity reduced	0.9%	1.4%	
	Sham		30.1%				Retinal artery occlusion	0.9%	0	
	Subgroups						Retinal tear	0	1.4%	
	Baseline VA		≥15 letters gained				Retinal vein occlusion	0	1.4%	
	VTE ≤20/200	VTE		67.9%	NR	60.7%	NR	Endophthalmitis	0.9%	0
		Sham		16.7%		22.2%		Corneal abrasion	0.9%	0
VTE >20/200	VTE		52.3%		53.5%		AE (24 to 52 weeks)	VTE	Sham	
	Sham		10.9%		32.7%		Patients with at least one serious adverse event	2.7%	3.3%	
Time since diagnosis						Vitreous haemorrhage	0.9%	1.7%		
VTE <2 mo	VTE		68.8%	NR	64.1%	NR	Glaucoma	0	1.7%	

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events			
	<i>Sham</i>		15.4%			34.6%	Iris neovascularisation	0	0	
	VTE ≥2 mo	<i>VTE</i>	38.8%			42.9%	Retinal haemorrhage	0	0	
	<i>Sham</i>		4.8%			19.0%	Visual acuity reduced	0	0	
	Perfusion status						Retinal artery occlusion	0	0	
	VTE perfused	<i>VTE</i>	58.4%	NS		58.4%	Retinal tear	0	1.7%	
		<i>Sham</i>	16%			30.0%	Retinal vein occlusion	0.9%	0	
	VTE non-perfused	<i>VTE</i>	51.4%			48.6%	Cataract	0.9%	0	
		<i>Sham</i>	4.3%			30.4%	Cystoid macular oedema	0.9%	0	
	CRT (µm):						Endophthalmitis	0	0	
		Baseline	24 weeks	p		52 weeks (all VTE PRN)	p	Corneal abrasion	0	0
	CRT							Reports of systemic adverse events were similar between groups; 2 deaths in the sham group by 24 weeks; 2.7% arterial thromboembolic events in the sham group and 0.9% in the intervention group		
	<i>VTE</i>	661.7 SD 237.4	-457.2	<0.001		-413.0	NS			
	<i>Sham</i>	672.4 SD 245.3	-144.8			-381.8				
	QoL									
		Baseline	24 weeks	p		52 weeks (all VTE PRN)	p			

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events
	PRN)						
	NEI-VFQ-25 total						
	<i>VTE</i>	77.76 SD 15.96	+7.2 SD 12.1	0.001	+7.5	NS	
	<i>Sham</i>	77.78 SD 16.25	+0.8 SD 9.8		+5.1		
	NEI-VFQ-25 near activities						
	<i>VTE</i>	69.96 SD 21.94	+8.3 SD 22.0	<0.05	+11.4	NS	
	<i>Sham</i>	70.72 SD 20.22	+1.84 SD 19.75		+8.3		
	NEI-VFQ-25 distance activities						
	<i>VTE</i>	75.99 SD 21.26	+6.1 SD 20.0	<0.05	+8.5	NS	
	<i>Sham</i>	78.08 SD 21.25	-0.64 SD 15.2		+3.8		
	NEI-VFQ-25 vision dependency						
	<i>VTE</i>	83.26 SD 25.51	+7.1 SD 20.5	<0.05	+6.0	NS	
	<i>Sham</i>	82.76 SD 27.41	+1.1 SD 20.5		+3.4		

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events																																																																																																																								
	Progression to neovascularisation: 0 with aflibercept, 6.8% with sham treatment over 52 weeks, p=0.006 Perfused status at week 24: 78.9% with aflibercept, 46.6% with sham treatment																																																																																																																									
GALILEO 2012^{36,37} 2 mg intravitreal aflibercept (every 4 weeks over 24 weeks) (n=103) versus sham injection (n=71) extension up to 52 weeks	BCVA (ETDRS letters): <table border="1" data-bbox="394 496 1436 1341"> <thead> <tr> <th></th> <th>Baseline</th> <th>24 weeks</th> <th>p</th> <th>52 weeks</th> <th>p</th> </tr> </thead> <tbody> <tr> <td colspan="6">BCVA (letters)</td> </tr> <tr> <td>VTE</td> <td>53.6 SD15.8</td> <td>+18.0</td> <td><0.0001</td> <td>+16.9</td> <td><0.0001</td> </tr> <tr> <td>Sham</td> <td>50.9 SD15.4</td> <td>+3.3</td> <td></td> <td>+3.8</td> <td></td> </tr> <tr> <td colspan="6">≥15 letters gained</td> </tr> <tr> <td>VTE</td> <td></td> <td>60.2%</td> <td><0.0001</td> <td>60.2%</td> <td>0.0004</td> </tr> <tr> <td>Sham</td> <td></td> <td>22.1%</td> <td></td> <td>32.4%</td> <td></td> </tr> <tr> <td colspan="6">≥10 letters lost</td> </tr> <tr> <td>VTE</td> <td></td> <td>7.8%</td> <td>0.0033</td> <td></td> <td></td> </tr> <tr> <td>Sham</td> <td></td> <td>25.0%</td> <td></td> <td></td> <td></td> </tr> <tr> <td colspan="6">Subgroups</td> </tr> <tr> <td colspan="2">Time since diagnosis</td> <td colspan="4">≥15 letters gained</td> </tr> <tr> <td>VTE <2 mo</td> <td></td> <td>70.9%</td> <td>NR</td> <td></td> <td></td> </tr> </tbody> </table>		Baseline	24 weeks	p	52 weeks	p	BCVA (letters)						VTE	53.6 SD15.8	+18.0	<0.0001	+16.9	<0.0001	Sham	50.9 SD15.4	+3.3		+3.8		≥15 letters gained						VTE		60.2%	<0.0001	60.2%	0.0004	Sham		22.1%		32.4%		≥10 letters lost						VTE		7.8%	0.0033			Sham		25.0%				Subgroups						Time since diagnosis		≥15 letters gained				VTE <2 mo		70.9%	NR			Ocular Adverse Events <table border="1" data-bbox="1501 496 2055 1341"> <thead> <tr> <th>AE</th> <th>VTE</th> <th>Sham</th> </tr> </thead> <tbody> <tr> <td>Discontinued treatment before week 24 because of AE</td> <td>1.9%</td> <td>11.3%</td> </tr> <tr> <td>Eye pain</td> <td>11.5%</td> <td>4.4%</td> </tr> <tr> <td>Conjunctival haemorrhage</td> <td>8.7%</td> <td>4.4%</td> </tr> <tr> <td>Retinal exudates</td> <td>6.7%</td> <td>7.4%</td> </tr> <tr> <td>Foreign body sensation</td> <td>5.8%</td> <td>7.4%</td> </tr> <tr> <td>Retinal vascular disorder</td> <td>5.8%</td> <td>8.8%</td> </tr> <tr> <td>Ocular hyperaemia</td> <td>4.8%</td> <td>5.9%</td> </tr> <tr> <td>Vitreous floaters</td> <td>4.8%</td> <td>0</td> </tr> <tr> <td>Macular oedema</td> <td>3.8%</td> <td>16.2%</td> </tr> <tr> <td>Macular ischaemia</td> <td>3.8%</td> <td>4.4%</td> </tr> <tr> <td>Optic disc vascular disorder</td> <td>3.8%</td> <td>4.4%</td> </tr> <tr> <td>Eye irritation</td> <td>2.9%</td> <td>10.3%</td> </tr> <tr> <td>Lacrimation increased</td> <td>2.9%</td> <td>5.9%</td> </tr> </tbody> </table>	AE	VTE	Sham	Discontinued treatment before week 24 because of AE	1.9%	11.3%	Eye pain	11.5%	4.4%	Conjunctival haemorrhage	8.7%	4.4%	Retinal exudates	6.7%	7.4%	Foreign body sensation	5.8%	7.4%	Retinal vascular disorder	5.8%	8.8%	Ocular hyperaemia	4.8%	5.9%	Vitreous floaters	4.8%	0	Macular oedema	3.8%	16.2%	Macular ischaemia	3.8%	4.4%	Optic disc vascular disorder	3.8%	4.4%	Eye irritation	2.9%	10.3%	Lacrimation increased	2.9%	5.9%
	Baseline	24 weeks	p	52 weeks	p																																																																																																																					
BCVA (letters)																																																																																																																										
VTE	53.6 SD15.8	+18.0	<0.0001	+16.9	<0.0001																																																																																																																					
Sham	50.9 SD15.4	+3.3		+3.8																																																																																																																						
≥15 letters gained																																																																																																																										
VTE		60.2%	<0.0001	60.2%	0.0004																																																																																																																					
Sham		22.1%		32.4%																																																																																																																						
≥10 letters lost																																																																																																																										
VTE		7.8%	0.0033																																																																																																																							
Sham		25.0%																																																																																																																								
Subgroups																																																																																																																										
Time since diagnosis		≥15 letters gained																																																																																																																								
VTE <2 mo		70.9%	NR																																																																																																																							
AE	VTE	Sham																																																																																																																								
Discontinued treatment before week 24 because of AE	1.9%	11.3%																																																																																																																								
Eye pain	11.5%	4.4%																																																																																																																								
Conjunctival haemorrhage	8.7%	4.4%																																																																																																																								
Retinal exudates	6.7%	7.4%																																																																																																																								
Foreign body sensation	5.8%	7.4%																																																																																																																								
Retinal vascular disorder	5.8%	8.8%																																																																																																																								
Ocular hyperaemia	4.8%	5.9%																																																																																																																								
Vitreous floaters	4.8%	0																																																																																																																								
Macular oedema	3.8%	16.2%																																																																																																																								
Macular ischaemia	3.8%	4.4%																																																																																																																								
Optic disc vascular disorder	3.8%	4.4%																																																																																																																								
Eye irritation	2.9%	10.3%																																																																																																																								
Lacrimation increased	2.9%	5.9%																																																																																																																								

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events		
	VTE ≥2 mo		50.0%				Papilloedema	1.9%	4.4%
	CRT (µm):						Retinal ischaemia	1.0%	4.4%
	Baseline	24 weeks	p	52 weeks	p	Visual acuity reduced	0	10.3%	
	CRT					IOP increased	9.6%	5.9%	
	VTE	683.2 SD234.5	-448.6	<0.0001	-423.5	<0.0001	Injection site pain	4.8%	2.9%
	Sham	638.7 SD224.7	-169.3		-219.3		Serious adverse events		
	QoL						At least 1 SAE	1.9%	5.9%
	Baseline	24 weeks	p	52 weeks	p	Glaucoma	0	2.9%	
	NEI-VFQ					Macular oedema	1.0%	1.5%	
	VTE		+7.5	0.0013		Retinal tear	1.0%	0	
	Sham		+3.5			Vitreous detachment	1.0%	0	
	Percentage of any patients progressing to any neovascularisation by week 24, difference between groups -1.5 (95% CI: -7.4 to 4.4)						Reports of systemic adverse events were similar between groups; no arterial thromboembolic events or deaths during 24 weeks		
	No significant differences on the EQ-5D score between groups						No endophthalmitis or cases of rhegmatogenous detachment, one incidence of uveitis in VTE group considered mild and resolved without change in therapy		

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events																																																						
PEGAPTANIB																																																								
<p>Wroblewski 2009³⁸⁻⁴⁴</p> <p>0.3 mg intravitreal pegaptanib sodium (every 6 weeks over 24 weeks) (n=33)</p> <p>versus 1 mg intravitreal pegaptanib sodium (every 6 weeks over 24 weeks) (n=33)</p> <p>versus sham injection (n=32)</p> <p>FU up to 52 weeks</p>	<p>BCVA (ETDRS letters):</p> <table border="1" data-bbox="394 402 1430 467"> <thead> <tr> <th></th> <th>Baseline</th> <th>30 weeks</th> <th>p</th> <th>52 weeks</th> <th>p</th> </tr> </thead> <tbody> <tr> <td colspan="6">BCVA (letters)</td> </tr> <tr> <td><i>PS 0.3 mg</i></td> <td>47.6</td> <td>+7.1</td> <td>NS, 0.09 vs sham</td> <td>+7.5</td> <td>NS vs sham</td> </tr> <tr> <td><i>PS 1 mg</i></td> <td>48.4</td> <td>+9.9</td> <td>0.02 vs sham</td> <td>+6.3</td> <td>NS vs sham</td> </tr> <tr> <td><i>Sham</i></td> <td>48.5</td> <td>-3.2</td> <td></td> <td>-2.4</td> <td></td> </tr> </tbody> </table> <p>≥15 letters gained</p> <table border="1" data-bbox="394 824 1430 987"> <thead> <tr> <th></th> <th>30 weeks</th> <th>p</th> </tr> </thead> <tbody> <tr> <td><i>PS 0.3 mg</i></td> <td>36%</td> <td>NS, p=0.48</td> </tr> <tr> <td><i>PS 1 mg</i></td> <td>39%</td> <td></td> </tr> <tr> <td><i>Sham</i></td> <td>28%</td> <td></td> </tr> </tbody> </table> <p>≥15 letters lost</p> <table border="1" data-bbox="394 1068 1430 1230"> <thead> <tr> <th></th> <th>30 weeks</th> <th>p</th> </tr> </thead> <tbody> <tr> <td><i>PS 0.3 mg</i></td> <td>9%</td> <td>0.03 vs sham</td> </tr> <tr> <td><i>PS 1 mg</i></td> <td>6%</td> <td>0.01 vs sham</td> </tr> <tr> <td><i>Sham</i></td> <td>31%</td> <td></td> </tr> </tbody> </table> <p>CRT (µm):</p>		Baseline	30 weeks	p	52 weeks	p	BCVA (letters)						<i>PS 0.3 mg</i>	47.6	+7.1	NS, 0.09 vs sham	+7.5	NS vs sham	<i>PS 1 mg</i>	48.4	+9.9	0.02 vs sham	+6.3	NS vs sham	<i>Sham</i>	48.5	-3.2		-2.4			30 weeks	p	<i>PS 0.3 mg</i>	36%	NS, p=0.48	<i>PS 1 mg</i>	39%		<i>Sham</i>	28%			30 weeks	p	<i>PS 0.3 mg</i>	9%	0.03 vs sham	<i>PS 1 mg</i>	6%	0.01 vs sham	<i>Sham</i>	31%		<p>No serious ocular adverse events up to week 30</p> <p>No endophthalmitis, traumatic cataract or retinal detachment (30 weeks)</p> <p>No evidence of sustained effect on intraocular pressure (30 weeks)</p> <p>No evidence of increased risk of systemic adverse events (30 weeks)</p>
	Baseline	30 weeks	p	52 weeks	p																																																			
BCVA (letters)																																																								
<i>PS 0.3 mg</i>	47.6	+7.1	NS, 0.09 vs sham	+7.5	NS vs sham																																																			
<i>PS 1 mg</i>	48.4	+9.9	0.02 vs sham	+6.3	NS vs sham																																																			
<i>Sham</i>	48.5	-3.2		-2.4																																																				
	30 weeks	p																																																						
<i>PS 0.3 mg</i>	36%	NS, p=0.48																																																						
<i>PS 1 mg</i>	39%																																																							
<i>Sham</i>	28%																																																							
	30 weeks	p																																																						
<i>PS 0.3 mg</i>	9%	0.03 vs sham																																																						
<i>PS 1 mg</i>	6%	0.01 vs sham																																																						
<i>Sham</i>	31%																																																							

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events			
	Baseline	30 weeks	p	52 weeks	p				
	CRT								
	PS 0.3 mg	688	-243	NS, p=0.13	-295	<0.05 vs sham			
	PS 1 mg	632	-179	NS, p=0.06	-216				
	Sham	674	-148			-183			
	3 patients in the sham arm and 1 patient in each of the pegaptanib sodium arms developed ocular neovascularisation (p=0.29 (NS))								
RANIBIZUMAB									
CRUISE 2010 ff. ^{10;45;46}	BCVA (ETDRS letters):					6 months			
	Baseline	6 months	12 months (ran PRN)		24 months (ran PRN, HORIZON)	AE	Ran 0.3 mg	Ran 0.5 mg	Sham
0.3 mg intravitreal ranibizumab (monthly for 6 months)	BCVA (letters, 95% CI)								
	Ran 0.3 mg	47.4	+12.7 (9.9, 15.4), p<0.0001 vs sham	+13.9 SD15.2, p=0.0007 vs sham	+8.2	Any intraocular inflammation event	2.3 %	1.6%	3.9%
	Ran 0.5 mg	48.1	+14.9 (12.6, 17.2), p<0.0001 vs sham	+13.9 SD14.2, p=0.0006 vs sham	+12.0	Iridocyclitis	0	0	0
versus 0.5 mg intravitreal ranibizumab (monthly for 6 months)	Sham	49.2	+0.8 (-2.0, 3.6)	+7.3 SD15.9	+7.6	Iritis	1.5%	1.6%	2.3%
		SD14.7				Vitritis	0.8%	0.8%	1.6%
						Endophthalmitis	0	0	0

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				Adverse events											
versus sham	≥15 letters gained				Lens damage	0	0	0								
extension 6 to 12 months 0.3 or 0.5 mg ranibizumab PRN	Ran 0.3 mg	46.2%, p<0.0001 vs sham	47.0%	38.6%	Cataract	1.5%	1.6%	0								
extension ≥12 to 24 months 0.5 mg ranibizumab PRN	Ran 0.5 mg	47.7%, p<0.0001 vs sham	50.8%	45.1%	Iris neovascularisation	1.5%	0.8%	7.0%								
	Sham	16.9%	33.1%	38.3%	Neovascular glaucoma	0	0	1.6%								
	≥15 letters lost				Rhegmatogenous retinal detachment	0	0	0								
	Ran 0.3 mg	3.8%	3.8%	12.9%	Retinal tear	0	0	0								
	Ran 0.5 mg	1.5%	2.3%	5.9%	Vitreous haemorrhage	3.8%	5.4%	7.0%								
	Sham	15.4%	10.0%	13.3%	Systemic adverse events balanced across groups; 1 myocardial infarction in each group, 1 transient ischaemic attack and angina pectoris in the same person in ran 0.5 mg group											
	Subgroups				12 months, sham for months 6 to 12											
	Time of diagnosis (6 month outcomes): <3 months: +13.2 letters (both ran groups), ≥3 months: +10.5 letters (0.3 mg ran), +15.3 letters (0.5 mg ran), p=?				<table border="1"> <thead> <tr> <th>Ocular AE</th> <th>Ran 0.3 mg</th> <th>Ran 0.5 mg</th> <th>Sham</th> </tr> </thead> <tbody> <tr> <td>Any intraocular inflammation</td> <td>2.3 %</td> <td>1.6%</td> <td>1.8%</td> </tr> </tbody> </table>				Ocular AE	Ran 0.3 mg	Ran 0.5 mg	Sham	Any intraocular inflammation	2.3 %	1.6%	1.8%
Ocular AE	Ran 0.3 mg	Ran 0.5 mg	Sham													
Any intraocular inflammation	2.3 %	1.6%	1.8%													
	Mean change in BCVA was greater for patients with worse baseline BCVA and CRT >450 μm															
	CRT (μm) and anatomic															
		Baseline	6 months	12 months (ran PRN)	24 months (ran PRN, HORIZON)											

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				Adverse events				
	CRT (μm, 95% CI)				event				
	Ran 0.3 mg	679.9 SD 242.4	-433.7 (-484.9, -382.6), p<0.0001 vs sham	-462.1, p= NS vs sham	-370.9				
	Ran 0.5 mg	688.7 SD 253.1	-452.3 (-497.0, -407.6), p<0.0001 vs sham	-452.8, p=NS vs sham	-412.2				
	Sham	687.0 SD 237.6	-167.7 (-221.5 -114.0)	-427.2	-418.7				
	CRT \leq250 μm								
	Ran 0.3 mg		75.0%, p<0.0001 vs sham	75.8%	58.0%				
	Ran 0.5 mg		76.9%, p<0.0001 vs sham	77.7%	56.9%				
	Sham		23.1%	70.8%	70.2%				
	No retinal haemorrhages								
	Ran 0.3 mg		0.8%	31.5%	41.3%				
	Ran 0.5 mg		1.5%	39.3%	47.8%				
	Sham		1.5%	5.4%	36.7%				
	QoL								
					HORIZON, 12 to 24 months				
					AE	Ran 0.3/0.5	Ran 0.5	Sham/ran 0.5 mg	
						0	0	0	
						0	0	0	
						3.8%	7.0%	1.8%	
						1.5%	3.9%	1.8%	
						0	0.8%	0	
						0	0	0	
						0	1.6%	1.8%	
						5.3%	5.4%	1.8%	
						0.8%	2.3%	0	

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events				
	Baseline	6 months	p	12 months (ran PRN)	p		mg	mg		
	NEI-VFQ (95% CI)									
	Ran 0.3 mg	+7.1 (5.2, 9.0)	<0.05 vs sham	+7.1	NS vs sham	Any ocular AE	62.6%	66.7%	62.5%	
	Ran 0.5 mg	+6.2 (4.3, 8.0)	<0.05 vs sham	+6.6	NS vs sham	Ocular AEs leading to discontinuation	1.9%	2.0%	0	
	Sham	+2.8 (0.8, 4.7)		+5.0		Cataract	5.6%	5.1%	3.1%	
						Ocular serious adverse events	9.3%	3.0%	5.2%	
						Cystoid macular oedema	0.9%	0	0	
						Endophthalmitis	1.9%	0	0	
						IOP increased	0.9%	0	0	
						Macular oedema	1.9%	2.0%	1.0%	
						Ischaemic optic neuropathy	0.9%	0	0	
						VA reduced	1.9%	1.0%	3.1%	
						VA reduced transiently	0.9%	0	0	
						Vitreous haemorrhage	0	0	1.0%	
						Arterial thromboembolic	1.9%	3.0%	2.1%	

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events																																																						
		events (potentially related to drug)																																																						
BEVACIZUMAB																																																								
Epstein 2012⁴⁷⁻⁴⁹ 1.25 mg intravitreal bevacizumab (4 injections over 6 months) (n=30) versus sham injection (n=30) 6 month open label extension (1.25 mg intravitreal bevacizumab (4 injections over 6 months) for all patients)	BCVA (ETDRS letters): <table border="1" data-bbox="380 527 1486 1339"> <thead> <tr> <th></th> <th>Baseline</th> <th>24 weeks</th> <th>p</th> <th>48 weeks (bev/bev vs sham/bev)</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>BCVA (letters)</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Bev</td> <td>44.4 SD15.3; 30% <34, 70% >34</td> <td>+14.1</td> <td><0.01</td> <td>+16.1</td> <td><0.05</td> </tr> <tr> <td>Sham</td> <td>43.9 SD16.0; 33.3% <34, 66.7% >34</td> <td>-2.0</td> <td></td> <td>+4.6</td> <td></td> </tr> <tr> <td>≥15 letters gained</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Bev</td> <td></td> <td>60%</td> <td>0.003</td> <td>60%</td> <td><0.05</td> </tr> <tr> <td>Sham</td> <td></td> <td>20%</td> <td></td> <td>33.3%</td> <td></td> </tr> <tr> <td>>15 letters lost</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Bev</td> <td></td> <td>6.7%</td> <td>NS, p=0.146</td> <td>6.7%</td> <td>NS</td> </tr> </tbody> </table>		Baseline	24 weeks	p	48 weeks (bev/bev vs sham/bev)	p	BCVA (letters)						Bev	44.4 SD15.3; 30% <34, 70% >34	+14.1	<0.01	+16.1	<0.05	Sham	43.9 SD16.0; 33.3% <34, 66.7% >34	-2.0		+4.6		≥15 letters gained						Bev		60%	0.003	60%	<0.05	Sham		20%		33.3%		>15 letters lost						Bev		6.7%	NS, p=0.146	6.7%	NS	Adverse events: Neovascularisation: 16.7% (sham) versus 0 (bev) had developed iris rubeosis at week 24; iris rubeosis regressed in all patients at week 48, no new cases in either group No events of endophthalmitis, retinal tear, retinal detachment; no serious non-ocular adverse events
	Baseline	24 weeks	p	48 weeks (bev/bev vs sham/bev)	p																																																			
BCVA (letters)																																																								
Bev	44.4 SD15.3; 30% <34, 70% >34	+14.1	<0.01	+16.1	<0.05																																																			
Sham	43.9 SD16.0; 33.3% <34, 66.7% >34	-2.0		+4.6																																																				
≥15 letters gained																																																								
Bev		60%	0.003	60%	<0.05																																																			
Sham		20%		33.3%																																																				
>15 letters lost																																																								
Bev		6.7%	NS, p=0.146	6.7%	NS																																																			

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				Adverse events
	<i>Sham</i>	23.3%	6.7%		
	Subgroups				
	Disease duration	BCVA (letters)			
	<i>Bev <90 days</i>	+18.7	0.039		
	<i>Bev >90 days</i>	+9.8			
	Age	BCVA (letters)			
	<i><70 years</i>	+14.2		NS, >0.05	
	<i>>70 years</i>	+7.4			
	<i><70 years sham/bev</i>	-1.4		<0.003	
	<i>>70 years sham/bev</i>	+20.1			
	CRT (µm):				
	Baseline	24 weeks	p	48 weeks (bev/bev vs sham/bev)	p

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events
	CRT					
	<i>Bev/bev</i>	712 SD330	-426	<0.001	-435	NS, >0.05
	<i>Sham/bev</i>	729 SD195	-102		-404	
	No residual oedema (CRT <300 μm)					
	<i>Bev/bev</i>		86.7%	<0.001	83.3%	NS
	<i>Sham/bev</i>		20%		60%	

Abbreviations: AE – adverse event, BCVA – best corrected visual acuity, CI – confidence interval, CRT – central retinal thickness, CRVO – central retinal vein occlusion, ETDRS – Early Treatment Diabetic Retinopathy Study, FU – follow-up, IQR – interquartile range, IOP – intraocular pressure, mo – months, NR – not reported, NS – non-significant, OCT – optical coherence tomography, PRN – pro re nata (as needed), QoL – quality of life, SD – standard deviation

Table 3: Study quality

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
DEXAMETHASONE							
GENEVA 2010 ff.	Low	Low	Partial: patients and assessors of efficacy variables	Low: ITT analysis, 94% FU at 6 months	Low	<i>Power:</i> 81% power to detect difference in primary outcome with n=495 for each trial <i>Similarity at baseline:</i> yes	Allergan Inc.
TRIAMCINOLONE							
SCORE 2009 ff	Low	Unclear	Partial (physicians and patients masked to dose but not triamcinolone versus observation)	Low: ITT analysis, 83 to 90% FU at 12 months	Low	<i>Power:</i> 80% power to detect difference in primary outcome with n=486 (but only 271 randomised) <i>Similarity at baseline:</i> yes	National Eye Institute grants, Allergan

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
ROVO 2013	Low	Low	Unclear	Low: ITT analysis (?), 92% FU at 12 months	Low	<i>Power:</i> 80% power to detect difference in primary outcome with n=53 per group (but only 20 to 38 per group) <i>Similarity at baseline:</i> unclear <i>Other:</i> limited baseline data	Jubiläumsfonds der Österreichischen Nationalbank, Ludwig Boltzmann Institute for Retinology and Biomicroscopic Laser Surgery (non-commercial)
AFLIBERCEPT							
COPERNICUS 2012	Low	Unclear	Low: double-blind	Low: ITT analysis, 89.9% assessed at primary end point	Low	<i>Power:</i> 90% power to detect difference in primary outcome with n=165 <i>Similarity at baseline:</i> yes	Bayer HealthCare, Regeneron Pharmaceuticals

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
GALILEO 2012	Unclear	Unclear	Low: double-blind	Low: ITT analysis, 86% assessed at primary end point	Low	Power: 90% power to detect difference in primary outcome with n=150 Similarity at baseline: yes	Bayer HealthCare, Regeneron Pharmaceuticals
PEGAPTANIB							
Wroblewski 2009	Low	Low	Low: patients and ophthalmologist responsible for patients care and assessments	Low: ITT analysis, 7% withdrawals	Low	Power: 80% power to detect difference in primary outcome with n=30 per group Similarity at baseline: yes	Eyetech Inc, Pfizer Inc.
RANIBIZUMAB							
CRUISE 2010 ff	Low	Unclear	Low: patients and evaluating examiners, injecting physicians masked to dose	Low: ITT analysis, 88.5 to 97.7% completed 6 months	Low	Power: not reported Similarity at baseline: yes	Genentech Inc.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
BEVACIZUMAB							
Epstein 2012	Unclear	Low	Low: patients, outcome assessors	Low: ITT analysis; missing data for 2 patients (primary endpoint)	Low	<i>Power:</i> 80% power to detect difference in primary outcome with n=24 per group <i>Similarity at baseline:</i> yes	Unclear; authors are consultants for Allergan, Novartis, Alcon, Bayer

For peer review only

Table 4: On-going trials

Study	Participants and baseline values	Intervention / Outcomes
<p data-bbox="176 371 342 396">MINOCYCLINE</p> <p data-bbox="176 431 806 456">http://clinicaltrials.gov/ct2/show/study/NCT01468844</p> <p data-bbox="176 492 226 516">USA</p> <p data-bbox="176 607 726 667">Study aim: to test the safety and effectiveness of minocycline as a treatment for CRVO</p> <p data-bbox="176 699 464 724">Design: RCT, double-blind</p> <p data-bbox="176 756 426 781">Follow-up: 24 months</p>	<p data-bbox="827 431 905 456">N: ~20</p> <p data-bbox="827 548 1419 643">Inclusion criteria:>18 years, macular oedema secondary to CRVO, CRT >350 µm, media clarity and pupillary dilatation sufficient for fundus photographs</p> <p data-bbox="827 675 1451 1003">Exclusion criteria: macular oedema due to causes other than CRVO, history of recurrent RVO or RVO >18 months, any other ocular condition that could affect macular oedema or BCVA, substantial cataract, photocoagulation within 4 months before study, pars plana vitrectomy within 6 months, major ocular surgery within 3 months, study eye treated with intravitreal or periocular steroid injections within 3 months, study eye treated with intravitreal anti-VEGF agents within 28 days; significant systemic disease (details given)</p>	<p data-bbox="1476 431 1902 558">Mino: 100 mg oral minocycline twice daily over 24 months; monthly bevacizumab injection over 3 months, then PRN</p> <p data-bbox="1476 591 1902 685">Placebo: oral placebo twice daily over 24 months; monthly bevacizumab injection over 3 months, then PRN</p> <p data-bbox="1476 776 1850 836">Primary end point: BCVA over 12 months</p> <p data-bbox="1476 868 1877 928">Other outcomes: number of bevacizumab injections, CRT, safety</p> <p data-bbox="1476 961 1871 1021">Outcome assessment: 6, 12, 18, 24 months</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Participants and baseline values	Intervention / Outcomes
<p>BEVACIZUMAB / TRIAMCINOLONE</p> <p>http://clinicaltrials.gov/show/NCT00566761</p> <p>Mexico</p> <p>Study aim: to assess if treatment of macular oedema secondary to CRVO is more effective with combined therapy of bevacizumab and triamcinolone compared to bevacizumab alone</p> <p>Design: RCT, open-label, phase 4</p> <p>Follow-up: 12 months</p>	<p>N: ~10</p> <p>Inclusion criteria: macular oedema secondary to CRVO; BCVA <20/40; CRT >250 µm (OCT)</p> <p>Exclusion criteria: diabetic retinopathy or other retinopathy; media opacity that does not allow follow-up; steroid responder; diagnosed glaucoma or IOP > 21 mmHg</p>	<p>Bev: bevacizumab 2.5 mg for (3 applications, administered monthly)</p> <p>Bev/Tria: bevacizumab 2.5 mg + triamcinolone 4 mg first dose followed by two doses of bevacizumab alone</p> <p>Primary end point: BCVA over 12 months</p> <p>Other outcomes: treatment complications</p> <p>Outcome assessment: 3, 6 and 12 months</p>
<p>RANIBIZUMAB</p>		

Study	Participants and baseline values	Intervention / Outcomes
<p data-bbox="176 315 684 341">http://clinicaltrials.gov/show/NCT01123564</p> <p data-bbox="176 373 275 399">Hungary</p> <p data-bbox="176 490 789 652">Study aim: to assess if ranibizumab (Lucentis) injection applied into the eye is superior to conventional treatment concerning the prevention of visual loss in patients having clinically significant macular oedema secondary to retinal vein occlusion</p> <p data-bbox="176 685 541 711">Design: RCT, open-label, phase 2</p> <p data-bbox="176 743 424 769">Follow-up: 12 months</p>	<p data-bbox="827 315 905 341">N: ~40</p> <p data-bbox="827 431 1449 691">Inclusion criteria: >18 years, macular oedema persisting for >3 months despite conventional medication; CRVO confirmed by slit-lamp biomicroscopy and fluorescein angiography (FLAG); patient in ranibizumab group do not receive macular laser treatment; CRT > 280 µm and/or retinal thickness is >330 µm at any region of the macula; baseline VA <64 ETDRS letters (or 0.4 decimal equivalent)</p> <p data-bbox="827 724 1449 1081">Exclusion criteria: diabetes mellitus; additional vitreoretinal diseases; history of pars plana vitrectomy; previous macular grid laser treatment; intravitreal triamcinolone acetonide treatment; complicated cataract surgery; advanced glaucomatous damage of optic nerve head; cataract (except mild, defined as grade 1 nuclear sclerosis and/or grade 1 posterior subcapsular cataract); age-related macular degeneration; pregnancy and lactation; women in childbearing potential who are not using double safe contraception</p>	<p data-bbox="1478 315 1911 477">Rani: intravitreal ranibizumab, applied monthly in the first 3 months, and after this only if visual acuity (VA) decreases with more than 5 letters at any monthly visits</p> <p data-bbox="1478 509 1898 672">Laser: Argon laser treatment; conventional grid pattern argon laser treatment and panretinal argon laser photocoagulation in an as needed basis</p> <p data-bbox="1478 753 1852 818">Primary end point: BCVA over 12 months</p> <p data-bbox="1478 850 1722 876">Other outcomes: CRT</p> <p data-bbox="1478 909 1894 935">Outcome assessment: monthly visits</p>

References

- 1
2
3
4
5
6
7 (1) Deramo VA, Cox TA, Syed AB, Lee PP, Fekrat S. Vision-related quality of life in people with
8 central retinal vein occlusion using the 25-item National Eye Institute Visual Function
9 Questionnaire. *Arch Ophthalmol* 2003; 121(9):1297-1302.
- 10
11 (2) McIntosh RL, Rogers SL, Lim L, Cheung N, Wang JJ, Mitchell P et al. Natural history of
12 central retinal vein occlusion: an evidence-based systematic review. *Ophthalmology* 2010;
13 117(6):1113-1123.
- 14
15 (3) Mitchell P, Smith W, Chang A. Prevalence and associations of retinal vein occlusion in
16 Australia. The Blue Mountains Eye Study. *Arch Ophthalmol* 1996; 114(10):1243-1247.
- 17
18 (4) Rogers S, McIntosh RL, Cheung N, Lim L, Wang JJ, Mitchell P et al. The prevalence of retinal
19 vein occlusion: pooled data from population studies from the United States, Europe, Asia,
20 and Australia. *Ophthalmology* 2010; 117(2):313-319.
- 21
22 (5) The Royal College of Ophthalmology. Interim guidelines for management of retinal vein
23 occlusion. [http://www.rcophth.ac.uk/core/core_picker/download](http://www.rcophth.ac.uk/core/core_picker/download.asp?id=728&filetitle=Interim+Guidelines+for+Management+of+Retinal+Vein+Occlusion+2010)
24 [asp?id=728&filetitle=Interim+Guidelines+for+Management+of+Retinal+Vein+Occlusion+2](http://www.rcophth.ac.uk/core/core_picker/download.asp?id=728&filetitle=Interim+Guidelines+for+Management+of+Retinal+Vein+Occlusion+2010)
25 010 [2010 [cited 2013 Sept. 7];
- 26
27 (6) Hayreh SS, Podhajsky PA, Zimmerman MB. Natural history of visual outcome in central
28 retinal vein occlusion. *Ophthalmology* 2011; 118(1):119-133.
- 29
30 (7) Kiire CA, Chong NV. Managing retinal vein occlusion. *BMJ* 2012; 344:e499.
- 31
32 (8) The Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema
33 in branch vein occlusion. *Am J Ophthalmol* 1984; 98(3):271-282.
- 34
35 (9) The Central Vein Occlusion Study Group. Evaluation of grid pattern photocoagulation for
36 macular edema in central vein occlusion. *Ophthalmology* 1995; 102(10):1425-1433.
- 37
38 (10) Brown DM, Campochiaro PA, Singh RP, Li Z, Gray S, Saroj N et al. Ranibizumab for macular
39 edema following central retinal vein occlusion: six-month primary end point results of a
40 phase III study. *Ophthalmology* 2010; 117(6):1124-1133.
- 41
42 (11) Haller JA, Bandello F, Belfort R, Jr., Blumenkranz MS, Gillies M, Heier J et al. Randomized,
43 sham-controlled trial of dexamethasone intravitreal implant in patients with macular
44 edema due to retinal vein occlusion. *Ophthalmology* 2010; 117(6):1134-1146.
- 45
46 (12) Cunningham MA, Edelman JL, Kaushal S. Intravitreal steroids for macular edema: the past,
47 the present, and the future. *Surv Ophthalmol* 2008; 53(2):139-149.
- 48
49 (13) Miller JW, Le CJ, Strauss EC, Ferrara N. Vascular endothelial growth factor A in intraocular
50 vascular disease. *Ophthalmology* 2013; 120(1):106-114.
- 51
52 (14) Ford JA, Lois N, Royle P, Clar C, Shyangdan D, Waugh N. Current treatments in diabetic
53 macular oedema: systematic review and meta-analysis. *BMJ Open* 2013; 3(3).
- 54
55
56
57
58
59
60

- 1
2
3 (15) Shyangdan D, Cummins E, Lois N, Royle P, Waugh N. Dexamethasone implants in the
4 treatment of macular oedema due to retinal vein occlusion: a single technology appraisal.
5 <http://www.nice.org.uk/nicemedia/live/13037/52883/52883.pdf> . 2010. Aberdeen HTA
6 Group.
7
- 8 (16) Higgins J, Altman D, Gøtzsche PC, Jüni P, Moher D, Oxman AD et al. The Cochrane
9 Collaboration's tool for assessing risk of bias in randomised trials. *British Medical Journal*
10 2011; 343:d5928.
11
- 12 (17) Haller JA, Bandello F, Belfort R, Jr., Blumenkranz MS, Gillies M, Heier J et al.
13 Dexamethasone intravitreal implant in patients with macular edema related to branch or
14 central retinal vein occlusion twelve-month study results. *Ophthalmology* 2011;
15 118(12):2453-2460.
16
- 17 (18) Yeh WS, Haller JA, Lanzetta P, Kuppermann BD, Wong TY, Mitchell P et al. Effect of the
18 duration of macular edema on clinical outcomes in retinal vein occlusion treated with
19 dexamethasone intravitreal implant. *Ophthalmology* 2012; 119(6):1190-1198.
20
- 21 (19) Bhavsar AR, Ip MS, Glassman AR, DRCRnet and the SCORE Study Groups. The risk of
22 endophthalmitis following intravitreal triamcinolone injection in the DRCRnet and SCORE
23 clinical trials. *American Journal of Ophthalmology* 2007; 144(3):454-456.
24
- 25 (20) Blodi BA, Domalpally A, Scott IU, Ip MS, Oden NL, Elledge J et al. Standard Care vs
26 Corticosteroid for Retinal Vein Occlusion (SCORE) Study system for evaluation of
27 stereoscopic color fundus photographs and fluorescein angiograms: SCORE Study Report
28 9. *Archives of Ophthalmology* 2010; 128(9):1140-1145.
29
- 30 (21) Chan CK, Ip MS, VanVeldhuisen PC, Oden NL, Scott IU, Tolentino MJ et al. SCORE Study
31 report #11: incidences of neovascular events in eyes with retinal vein occlusion.
32 *Ophthalmology* 2011; 118(7):1364-1372.
33
- 34 (22) Ip M, Oden N, VanVeldhuisen P, Scott I, Blodi B. The Standard Care vs. Corticosteroid for
35 Retinal Vein Occlusion Study: Design and Baseline Characteristics. *American Academy of*
36 *Ophthalmology* 2008;260.
37
- 38 (23) Ip MS, Scott IU, VanVeldhuisen PC, Oden NL, Blodi BA, Fisher M et al. A randomized trial
39 comparing the efficacy and safety of intravitreal triamcinolone with observation to treat
40 vision loss associated with macular edema secondary to central retinal vein occlusion: the
41 Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5. *Archives*
42 *of Ophthalmology* 2009; 127(9):1101-1114.
43
- 44 (24) Ip MS, Oden NL, Scott IU, VanVeldhuisen PC, Blodi BA, Figueroa M et al. SCORE Study
45 report 3: study design and baseline characteristics. *Ophthalmology* 2009; 116(9):1770-
46 1777.
47
- 48 (25) Myers D, Blodi B, Ip M, Scott I, Warren K. Reading Center Evaluation of OCT Images From
49 Patients Enrolled in the Standard Care vs. Corticosteroid for Retinal Vein Occlusion
50 (SCORE) Study. *IOVS* 2006; 47:ARVO.
51
- 52 (26) Oden NL, Veldhuisen PC, Scott IU, Ip MS, Blodi BA. Temporal Variability of OCT in Retinal
53 Vein Occlusion Participants in the SCORE Study. *IOVS* 2007; 48:ARVO.
54
55
56
57
58
59
60

- 1
2
3 (27) Scott IU, VanVeldhuisen PC, Oden NL, Ip MS, Blodi BA, Jumper JM et al. SCORE Study
4 report 1: baseline associations between central retinal thickness and visual acuity in
5 patients with retinal vein occlusion. *Ophthalmology* 2009; 116(3):504-512.
6
- 7 (28) Scott IU, Blodi BA, Ip MS, VanVeldhuisen PC, Oden NL, Chan CK et al. SCORE Study Report
8 2: Interobserver agreement between investigator and reading center classification of
9 retinal vein occlusion type. *Ophthalmology* 2009; 116(4):756-761.
10
- 11 (29) Scott IU, Oden NL, VanVeldhuisen PC, Ip MS, Blodi BA, Antoszyk AN et al. SCORE Study
12 Report 7: incidence of intravitreal silicone oil droplets associated with staked-on vs luer
13 cone syringe design. *American Journal of Ophthalmology* 2009; 148(5):725-732.
14
- 15 (30) Scott IU, VanVeldhuisen PC, Oden NL, Ip MS, Blodi BA, Hartnett ME et al. Baseline
16 predictors of visual acuity and retinal thickness outcomes in patients with retinal vein
17 occlusion: Standard Care Versus Corticosteroid for Retinal Vein Occlusion Study report 10.
18 *Ophthalmology* 2011; 118(2):345-352.
19
- 20 (31) Scott IU, VanVeldhuisen PC, Oden NL, Ip MS, Domalpally A, Doft BH et al. Baseline
21 characteristics and response to treatment of participants with hemiretinal compared with
22 branch retinal or central retinal vein occlusion in the Standard Care vs Corticosteroid for
23 Retinal Vein Occlusion (SCORE) study: SCORE Study Report 14. *Archives of Ophthalmology*
24 2012; 130(12):1517-1524.
25
- 26 (32) Warren K, Blodi BA, Oden N, Veldhuisen P, Scott IU, Ip M. Reading Center Evaluation of
27 Baseline Retinal Images in the Standard Care vs. Corticosteroid for Retinal Vein Occlusion
28 (SCORE) Study. *Iovs* 2008;ARVO.
29
- 30 (33) Aggermann T, Brunner S, Krebs I, Haas P, Womastek I, Brannath W et al. A prospective,
31 randomised, multicenter trial for surgical treatment of central retinal vein occlusion:
32 results of the Radial Optic Neurotomy for Central Vein Occlusion (ROVO) study group.
33 *Graefes Arch Clin Exp Ophthalmol* 2013; 251(4):1065-1072.
34
- 35 (34) Boyer D, Heier J, Brown DM, Clark WL, Vitti R, Berliner AJ et al. Vascular endothelial
36 growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-
37 month results of the phase 3 COPERNICUS study. *Ophthalmology* 2012; 119(5):1024-1032.
38
- 39 (35) Brown DM, Heier JS, Clark WL, Boyer DS, Vitti R, Berliner AJ et al. Intravitreal aflibercept
40 injection for macular edema secondary to central retinal vein occlusion: 1-Year Results
41 From the Phase 3 COPERNICUS Study. *American Journal of Ophthalmology* 2013;
42 155(3):429-437.
43
- 44 (36) Gillies M. Intravitreal vegf trap-eye in central retinal vein occlusion: Results of the phase 3
45 copernicus and galileo studies. *Clinical and Experimental Ophthalmology* 2012; 40:44.
46
- 47 (37) Holz FG, Roider J, Ogura Y, Korobelnik JF, Simader C, Groetzbach G et al. VEGF Trap-Eye for
48 macular oedema secondary to central retinal vein occlusion: 6-month results of the phase
49 III GALILEO study. *British Journal of Ophthalmology* 2013; 97(3):278-284.
50
- 51 (38) Ciulla TA. Treatment of Macular Edema Following Central Retinal Vein Occlusion With
52 Pegaptanib Sodium (Macugen): A One-Year Study. *American Academy of Ophthalmology*
53 2007;199.
54
55
56
57
58
59
60

- 1
2
3 (39) Csaky KG. Pegaptanib (Macugen) for Macular Edema in Central Retinal Vein Occlusion:
4 Early OCT Results and Effect of Therapy Reinitiation. *American Academy of Ophthalmology*
5 2007;269.
6
7 (40) Patel SS. Pegaptanib Sodium for the Treatment of Macular Edema Following Central
8 Retinal Vein Occlusion (CRVO): Anatomical Outcomes. *Iovs* 2007; 48:ARVO.
9
10 (41) Wells JA. Pegaptanib Sodium for Treatment of Macular Edema Secondary to Central
11 Retinal Vein Occlusion (CRVO). *Iovs* 2006; 47:ARVO.
12
13 (42) Wells JA. Safety and Efficacy of Pegaptanib Sodium in Treating Macular Edema Secondary
14 to Central Retinal Vein Occlusion. *American Academy of Ophthalmology* 2006;288.
15
16 (43) Wells JA, Wroblewski JJ. Pegaptanib Sodium for the Treatment of Macular Edema
17 Following Central Retinal Vein Occlusion (CRVO): Functional Outcomes. *Iovs* 2007;
18 48:ARVO.
19
20 (44) Wroblewski JJ, Wells JA, III, Adamis AP, Buggage RR, Cunningham ET, Jr., Goldbaum M et
21 al. Pegaptanib sodium for macular edema secondary to central retinal vein occlusion.
22 *Archives of Ophthalmology* 2009; 127(4):374-380.
23
24 (45) Campochiaro PA, Brown DM, Awh CC, Lee SY, Gray S, Saroj N et al. Sustained benefits from
25 ranibizumab for macular edema following central retinal vein occlusion: twelve-month
26 outcomes of a phase III study. *Ophthalmology* 2011; 118(10):2041-2049.
27
28 (46) Heier JS, Campochiaro PA, Yau L, Li Z, Saroj N, Rubio RG et al. Ranibizumab for macular
29 edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial.
30 *Ophthalmology* 2012; 119(4):802-809.
31
32 (47) Epstein D, Algvere P, Von WG, Seregard S, Kvanta A. Long-term benefit from bevacizumab
33 for macular edema in central retinal vein occlusion: 12-month results of a prospective
34 study. *Acta Ophthalmologica* 2012; 90:48.
35
36 (48) Epstein DL, Algvere PV, Von WG, Seregard S, Kvanta A. Benefit from bevacizumab for
37 macular edema in central retinal vein occlusion: twelve-month results of a prospective,
38 randomized study. *Ophthalmology* 2012; 119(12):2587-2591.
39
40 (49) Epstein DL, Algvere PV, Von WG, Seregard S, Kvanta A. Bevacizumab for macular edema in
41 central retinal vein occlusion: a prospective, randomized, double-masked clinical study.
42 *Ophthalmology* 2012; 119(6):1184-1189.
43
44 (50) Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and
45 bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011;
46 364(20):1897-1908.
47
48 (51) Campbell RJ, Gill SS, Bronskill SE, Paterson JM, Whitehead M, Bell CM. Adverse events with
49 intravitreal injection of vascular endothelial growth factor inhibitors: nested case-control
50 study. *BMJ* 2012; 345:e4203.
51
52 (52) Curtis LH, Hammill BG, Schulman KA, Cousins SW. Risks of mortality, myocardial infarction,
53 bleeding, and stroke associated with therapies for age-related macular degeneration.
54 *Archives of Ophthalmology* 2010; 128(10):1273-1279.
55
56
57
58
59
60

- 1
2
3 (53) Hwang DJ, Kim YW, Woo SJ, Park KH. Comparison of systemic adverse events associated
4 with intravitreal anti-VEGF injection: ranibizumab versus bevacizumab. *J Korean Med Sci*
5 2012; 27(12):1580-1585.
6
- 7 (54) Sharma S, Johnson D, Abouammoh M, Hollands S, Brissette A. Rate of serious adverse
8 effects in a series of bevacizumab and ranibizumab injections. *Can J Ophthalmol* 2012;
9 47(3):275-279.
10
- 11 (55) Micieli JA, Micieli A, Smith AF. Identifying systemic safety signals following intravitreal
12 bevacizumab: systematic review of the literature and the Canadian Adverse Drug Reaction
13 Database. *Can J Ophthalmol* 2010; 45(3):231-238.
14
- 15 (56) Choi DY, Ortube MC, McCannel CA, Sarraf D, Hubschman JP, McCannel TA et al. Sustained
16 elevated intraocular pressures after intravitreal injection of bevacizumab, ranibizumab,
17 and pegaptanib. *Retina* 2011; 31(6):1028-1035.
18
- 19 (57) Good TJ, Kimura AE, Mandava N, Kahook MY. Sustained elevation of intraocular pressure
20 after intravitreal injections of anti-VEGF agents. *Br J Ophthalmol* 2011; 95(8):1111-1114.
21
- 22 (58) Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S et al.
23 Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration:
24 one-year findings from the IVAN randomized trial. *Ophthalmology* 2012; 119(7):1399-
25 1411.
26
- 27 (59) Ford JA, Elders A, Shyangdan D, Royle P, Waugh N. The relative clinical effectiveness of
28 ranibizumab and bevacizumab in diabetic macular oedema: an indirect comparison in a
29 systematic review. *BMJ* 2012; 345:e5182.
30
- 31 (60) Stewart MW. Aflibercept (VEGF Trap-eye): the newest anti-VEGF drug. *Br J Ophthalmol*
32 2012; 96(9):1157-1158.
33
- 34 (61) Braithwaite T, Nanji AA, Greenberg PB. Anti-vascular endothelial growth factor for macular
35 edema secondary to central retinal vein occlusion. *Cochrane Database Syst Rev*
36 2010;(10):CD007325.
37
- 38 (62) Gewaily D, Greenberg PB. Intravitreal steroids versus observation for macular edema
39 secondary to central retinal vein occlusion. *Cochrane Database Syst Rev*
40 2009;(1):CD007324.
41
- 42 (63) Lazo-Langner A, Hawel J, Ageno W, Kovacs MJ. Low molecular weight heparin for the
43 treatment of retinal vein occlusion: a systematic review and meta-analysis of randomized
44 trials. *Haematologica* 2010; 95(9):1587-1593.
45
- 46 (64) Squizzato A, Manfredi E, Bozzato S, Dentali F, Ageno W. Antithrombotic and fibrinolytic
47 drugs for retinal vein occlusion: a systematic review and a call for action. *Thromb Haemost*
48 2010; 103(2):271-276.
49
50
51
52
53
54
55
56
57
58
59
60

Appendix 1: Search strategy

CRVO: Clinical effectiveness search for RCTs and SRs**Ovid MEDLINE(R) 1946 to March Week 1 2013, searched on 20 March 2013**

- 1 CRVO.mp.
- 2 Retinal Vein Occlusion/
- 3 retinal vein occlusion.mp.
- 4 retinal vein obstruction.mp.
- 5 retinal venous occlusion.mp.
- 6 retinal venous obstruction.mp.
- 7 retina*.mp.
- 8 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction").mp.
- 9 7 and 8
- 10 1 or 2 or 3 or 4 or 5 or 6 or 9
- 11 randomized controlled trial.pt.
- 12 (random* or "controlled trial*" or "clinical trial*" or rct).tw.
- 13 11 or 12
- 14 (metaanalys* or "meta analys*" or "meta-analys*").tw.
- 15 "systematic review*".tw.
- 16 meta analysis.pt.
- 17 14 or 15 or 16
- 18 10 and 13
- 19 10 and 17
- 20 18 or 19

1
2
3 21 limit 20 to yr="2005 -Current"
4
5
6
7
8

9 **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations March 19, 2013, searched on 20**
10 **March 2013**

11
12 1 CRVO.mp.
13

14 2 retinal vein occlusion.mp.
15

16 3 retinal vein obstruction.mp.
17

18 4 retinal venous occlusion.mp.
19

20 5 retinal venous obstruction.mp.
21

22 6 retina*.mp.
23

24 7 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central
25 venous obstruction").mp.
26
27

28 8 6 and 7
29

30 9 1 or 2 or 3 or 4 or 5 or 8
31

32 10 (random* or "controlled trial*" or "clinical trial*" or rct).tw.
33

34 11 (metaanalys* or "meta analys*" or "meta-analys*").tw.
35

36 12 "systematic review*".tw.
37

38 13 11 or 12
39

40 14 9 and 10
41

42 15 9 and 13
43

44 16 14 or 15
45
46
47
48
49
50
51

52 **Embase 1980 to 2013 Week 11, searched on 20 March 2013**
53

54 1 CRVO.mp.
55
56
57
58
59
60

- 1
2
3 2 Retina Vein Occlusion/
4
5 3 Central Retina Vein Occlusion/
6
7 4 retinal vein occlusion.mp.
8
9 5 retinal vein obstruction.mp.
10
11 6 retinal venous occlusion.mp.
12
13 7 retinal venous obstruction.mp.
14
15 8 retina*.mp.
16
17 9 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central
18 venous obstruction").mp.
19
20 10 8 and 9
21
22 11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 10
23
24 12 randomized controlled trial/
25
26 13 (random* or "controlled trial*" or "clinical trial*" or rct).tw.
27
28 14 12 or 13
29
30 15 systematic review/
31
32 16 meta analysis/
33
34 17 (metaanalys* or "meta analys*" or "meta-analys*").tw.
35
36 18 "systematic review*".tw.
37
38 19 15 or 16 or 17 or 18
39
40 20 11 and 14
41
42 21 11 and 19
43
44 22 20 or 21
45
46 23 limit 22 to yr="2005 -Current"
47
48
49
50
51
52
53
54

55 **Cochrane Library (including CDSR, CENTRAL, DARE, HTA, NHS EED), searched on 20 March 2013**

56 #1 CRVO
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- #2 MeSH descriptor: [Retinal Vein Occlusion] this term only
- #3 "retinal vein occlusion"
- #4 "retinal vein obstruction"
- #5 "retinal venous occlusion"
- #6 "retinal venous obstruction"
- #7 retina*
- #8 "central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction"
- #9 #7 and #8
- #10 #1 or #2 or #3 or #4 or #5 or #6 or #9
- #11 #10 from 2005

peer review only



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	68-71
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	23
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	25-35
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	56-59
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.



Treatments for macular oedema following central retinal vein occlusion: systematic review

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-004120.R1
Article Type:	Research
Date Submitted by the Author:	03-Jan-2014
Complete List of Authors:	Ford, John; University of East Anglia, Public Health Clar, Christine; Warwick University, Warwick Evidence Lois, Noemi; Centre for Vision and Vascular Science, Barton, Samantha; BMJ Technology Assessment Group, Thomas, Sian; Warwick University, Warwick Evidence Court, Rachel; Warwick University, Division of Health Sciences Shyangdan, Deepson; University of Warwick, Warwick Evidence, Warwick Medical School Waugh, Norman; University of Warwick, Warwick Evidence
Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Ophthalmology, Public health
Keywords:	Medical ophthalmology < OPHTHALMOLOGY, systematic review, anti-VEGF, Central retinal vein occlusion, macular oedema

SCHOLARONE™
Manuscripts

Only

1
2
3 **Treatments for macular oedema following central retinal vein occlusion:**
4 **systematic review**
5
6
7

8
9 **Authors**

10 John A. Ford, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich, UK
11 Christine Clar, Warwick Evidence, University of Warwick, Coventry, UK
12 Noemi Lois, Centre for Vision and Vascular Science, Queen's University, Belfast, UK
13 Samantha Barton, BMJ Technology Assessment Group, London, UK
14 Sian Thomas, Warwick Evidence, University of Warwick, Coventry, UK
15 Rachel Court, Warwick Evidence, University of Warwick, Coventry, UK
16 Deepson Shyangdan, Warwick Evidence, University of Warwick, Coventry, UK
17 Norman Waugh, Division of Health Sciences, Medical School, University of Warwick, Coventry, UK
18
19
20
21
22
23
24

25 **Corresponding author**

26 John Ford
27 Norwich Medical School
28 Faculty of Medicine and Health Sciences
29 University of East Anglia
30 Chancellors Drive
31 Norwich, NR4 7TJ
32
33
34
35
36
37
38
39
40
41
42

43 **Protocol:** Not published

44 **Words:** 5750 words

45 **Key words:** central retinal vein occlusion, aflibercept, ranibizumab, bevacizumab, dexamethasone,
46 pegaptanib, triamcinolone, systematic review, anti-VEGF, macular oedema
47

48 **Disclosure**

49 No additional data available.
50
51
52
53
54
55
56
57
58
59
60

Abstract

Objectives

To review systematically the randomised controlled trial (RCT) evidence for treatment of macular oedema due to central retinal vein occlusion (CRVO).

Data sources

MEDLINE, EMBASE, CDSR, DARE, HTA, NHSEED, CENTRAL and meeting abstracts (January 2005 to March 2013).

Study eligibility criteria, participants and interventions

RCTs with at least 12 months' follow-up assessing pharmacological treatments for CRVO were included with no language restrictions.

Study appraisal and synthesis methods

Two authors screened titles and abstracts and conducted data extracted and Cochrane risk of bias assessment. Meta-analysis was not possible due to lack of comparable studies.

Results

Eight studies (35 articles, 1714 eyes) were included, assessing aflibercept (n=2), triamcinolone (n=2), bevacizumab (n=1), pegaptanib (n=1), dexamethasone (n=1) and ranibizumab (n=1). In general, bevacizumab, ranibizumab, aflibercept and triamcinolone resulted in clinically significant increases in the proportion of participants with an improvement in visual acuity of ≥ 15 letters, with 40-60% gaining ≥ 15 letters on active drugs, compared to 12-28% with sham. Results for pegaptanib and dexamethasone were mixed. Steroids were associated with cataract formation and increased intra-ocular pressure. No overall increase in adverse events was found with bevacizumab, ranibizumab, aflibercept or pegaptanib compared to control. Quality of life was poorly reported. All studies had a low or unclear risk of bias.

Limitations

All studies evaluated a relatively short primary follow-up (1 year or less). Most had an unmasked extension phase. There was no head-to-head evidence. The majority of participants included had non-ischaemic CRVO.

Conclusions and implications of key findings

Bevacizumab, ranibizumab, aflibercept and triamcinolone appear to be effective in treating macular oedema secondary to CRVO. Long-term data on effectiveness and safety are needed. Head-to-head trials and research to identify “responders” is needed to help clinicians make the right choices for their patients. Research aimed to improve sight in people with ischaemic CRVO is required.

For peer review only

Article summary

Article focus

To review the clinical effectiveness of pharmacological treatments for central retinal vein occlusion.

Key messages

Bevacizumab, ranibizumab, aflibercept and triamcinolone have demonstrated good short-term clinical effectiveness in randomised controlled trials for the treatment of macular oedema secondary to central retinal vein occlusion.

Dexamethasone and pegaptanib have shown mixed results.

Strengths and limitations of this study

A robust systematic review method was used which only included randomised controlled trials.

There were no head-to-head trials and there was a lack of long-term data on both effectiveness and safety.

Introduction

Central retinal vein occlusion (CRVO) is a vascular disorder of the retina with often catastrophic consequences to vision and quality of life.^{1;2} The incidence of CRVO increases with age; most individuals affected are 50 years of age or older.³ It has been estimated that there are around 80 new cases of CRVO per million population per year.^{4;5} Although CRVO most commonly affects one eye, in around 10% of patients the disease affects both eyes.² Approximately 20% of patients with CRVO will develop large areas of retinal non-perfusion (ischaemia).⁶ Furthermore, a small proportion (around 8%) of patients with non-ischaemic CRVO may convert into the ischaemic type during follow-up.⁶ Retinal ischaemia may lead to the development of neovascularisation in the retina, iris or anterior chamber angle. Complications of neovascularisation include vitreous haemorrhage and neovascular glaucoma.⁶ Currently there is no treatment for ischaemic CRVO other than that aimed at ameliorating the severity of complications, with treatments such as panretinal photocoagulation. Even with the use of current therapies, some eyes with ischaemic CRVO end up blind and painful and, ultimately, enucleation (removal of the eye) is necessary to provide comfort to patients.

Not all people with CRVO will require treatment and macular oedema will resolve in about a third of those with non-ischaemic CRVO.^{2;7} However most will need treatment and the number of options has increased in recent years. Laser photocoagulation has been for many years the standard therapy for patients with macular oedema secondary to branch retinal vein obstruction (BRVO).⁸ However, laser treatment was not found to be beneficial to those with macular oedema secondary to CRVO;⁹ for these patients, no therapeutic modalities could be offered. Recently, several studies have demonstrated the benefit of anti-vascular endothelial growth factor (VEGF) therapies and steroids for the management of patients with macular oedema secondary to CRVO.^{10;11} Steroids, such as triamcinolone and dexamethasone, have anti-inflammatory and anti-proliferative attributes (as well as some anti-VEGF effects) and therefore are primarily effective by reducing the oedema of the macula.¹² Anti-VEGF treatments, such as bevacizumab, ranibizumab, aflibercept and pegaptanib, inhibit vascular endothelial growth factor A. In CRVO there is an increase in vascular endothelial growth factor A which leads to neovascularization and oedema.¹³ In the UK, NICE has approved dexamethasone (in the long-acting form, Ozurdex) and ranibizumab (Lucentis) and an appraisal of aflibercept is currently underway. Bevacizumab is also used, but is not licensed for use in the eye; however this is because the manufacturer has never sought a licence, preferring to market ranibizumab. Triamcinolone has also been used off-licence.

1
2
3 An up-to-date review incorporating all drug treatments for macular oedema secondary to CRVO is
4 needed. The purpose of this study is to review systematically the randomised controlled evidence
5 for drug treatments of macular oedema secondary to CRVO.
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Methods

A systematic review was conducted. The following databases were searched: MEDLINE, MEDLINE In-process, EMBASE (all via OVID); CDSR, DARE, HTA, NHSEED, CENTRAL (all via The Cochrane Library); Science Citation Index and Conference Proceedings Citation Index-Science (via Web of Knowledge). In addition to the bibliographic database searching, supplementary searches were undertaken to look for recent and unpublished studies in the WHO International Clinical Trials Registry Platform and ophthalmology conference websites (American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology from 2010 to 2012).

Search strategy

An iterative procedure was used to develop two search strategies with input from previous systematic reviews.^{14;15} The first search strategy was designed to retrieve articles reporting RCTs or systematic reviews about CRVO published from 2005 onwards (the publication date of the first RCT on triamcinolone in Medline). Terms for retinal vein occlusion were included to ensure identification of articles in which both BRVO and CRVO were covered, but were reported separately. The second strategy focussed on retrieving articles where adverse events of relevant pharmacological treatments for CRVO were reported. This second search was limited by condition (age-related macular degeneration (AMD) or RVO), study type (RCTs, SRs or observational studies) and date (published from 2010 onwards). Searches were conducted in March 2013. The strategies used in each database are provided in appendix 1. Auto alerts of searches were set up to capture relevant articles published after the dates of the searches.

Reference lists from the included studies and identified systematic reviews were screened.

Inclusion and exclusion criteria

RCTs were used to assess the clinical effectiveness and adverse events.

Only RCTs examining pharmacological treatment compared with laser treatment, observation, placebo (sham injection) or another pharmacological intervention with at least 12 months follow-up were included. Comparisons of different doses of drugs were not included unless there was an additional comparator group as defined above. Studies including CRVO and BRVO were included

1
2
3 providing participants with CRVO were reported as a subgroup. Studies assessing treatments aimed
4 at restoring circulation to the occluded vein shortly after onset (<30 days) were excluded. There
5 were no language restrictions.
6
7
8
9

10 *Outcomes*

11
12 The primary outcome was visual acuity measured as mean change in best corrected visual acuity
13 (BCVA) or as proportion of patients improving by 15 ETDRS (Early Treatment for Diabetic
14 Retinopathy Study) letters or more. Secondary outcomes included mean change in macular thickness
15 using optical coherence tomography (OCT), quality of life and adverse events.
16
17
18
19
20

21 *Screening and data extraction*

22
23 Search results were screened independently by two authors (CC, JF and ST). Differences were
24 resolved through discussion or by consulting a third author (JF). Data were extracted by one author
25 (CC and DS) and checked by a second (ST, CC). Data extraction included inclusion/exclusion criteria,
26 baseline demographics, mean change in BCVA, proportion of patients with 15 letters improvement,
27 central retinal thickness (CRT) and adverse events. Risk of bias was assessed by two reviewers using
28 the Cochrane risk of bias tool.¹⁶
29
30
31
32
33
34
35

36 Meta-analysis was not possible because of a lack of comparable studies.
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Results

Search results

The study flow is shown in figure 1. The electronic searches yielded 518 records. 475 were eliminated based on information in the titles and abstract. The full text of the remaining 43 records was checked, and a further eight were eliminated. Reasons for exclusion included the trial being a commentary rather than an RCT, the study having no relevant comparison group (dose ranging only), the participants did not have macular oedema secondary to CRVO, or the interventions being ineligible (non-pharmacological). The remaining 35 records (including conference abstracts) reported on eight RCTs of six different pharmacological agents, and these were included in the analysis. The Geneva study (2010)^{11,17,18} technically consists of two RCTs, but as these were analysed and reported together, it was counted as one RCT in this analysis.

We also identified three relevant ongoing trials, one investigating minocycline (<http://clinicaltrials.gov/ct2/show/study/NCT01468844>), one investigating a combination of bevacizumab and triamcinolone (<http://clinicaltrials.gov/show/NCT00566761>), and one investigating ranibizumab (<http://clinicaltrials.gov/show/NCT01123564>).

Study characteristics

Detailed study characteristics of the included studies are shown in table 1.

Study design

Of the eight included RCTs, six were described as double-blind and seven were sham-controlled. All but one were multicentre. Only one was not funded by industry. Four trials were international trials, two came from the USA, and one each from Austria and Sweden. Six of the trials measured primary end-points at around six months (24 to 30 weeks), whereas two measured primary end-points at 12 months. Five studies reported follow-up data for up to 12 months, and two reported data for follow-up periods of up to two years.

Participants

The trials randomised a total of 1714 eyes (one eye per person). The number of eyes per study ranged between 60 and 437. Follow-up at the primary end-point ranged from 77 to 98% (generally over 90% in the intervention groups). The participants had a mean age of between 59.0 and 70.5

1
2
3 years, and between 36 and 49% were female. Only two studies reported mean duration of macular
4 oedema (4.3 and 4.9 months). Five studies reported mean time since CRVO diagnosis (range 2.4 to
5 2.9 months). Mean baseline BCVA was between 44 and 52.5 ETDRS letters, baseline CRT was
6 between 569 and 721 μm . In most trials, the focus was on macular oedema secondary to CRVO only,
7 but in the Geneva trial macular oedema secondary to BRVO and CRVO was included and only limited
8 data were available on the CRVO-only group.
9
10

11 12 13 *Interventions*

14
15
16 The Geneva trial (2010 ff.)^{11;17;18} compared a 0.35 mg (n=136) and a 0.7 mg dexamethasone (n=154)
17 intravitreal implant with sham treatment (n=147). After the initial 6 month study period, patients
18 could enter a 6 month open label extension, where they received a 0.7 mg dexamethasone
19 intravitreal implant.
20
21

22
23 The SCORE trial (2009 ff.)¹⁹⁻³² compared intravitreal injections of 1 or 4 mg of triamcinolone (~2
24 injections over 12 months, n= 92 and 91 for 1 and 4 mg respectively) with an observation group
25 (n=88). Two forms of triamcinolone have been used in trial; the SCORE trial used Trivaris, rather than
26 Kenalog. Trivaris is no longer available because its manufacturer has promoted an alternative
27 steroid (dexamethasone). The ROVO trial (2013)³³ compared a single intravitreal injection of 4 mg of
28 triamcinolone (over 12 months, n=25) with radial optic neurotomy (n=38) or sham injection (n=20).
29
30

31
32 In the COPERNICUS trial (2012)^{34;35}, intravitreal injections of 2 mg of aflibercept (n=114) were given
33 every 4 weeks over 24 weeks to the intervention group and the comparison group received a sham
34 injection (n=75). During weeks 24 to 52, patients in both groups received aflibercept if they met
35 protocol-specified retreatment criteria, and received a sham injection if retreatment was not
36 indicated (3.9 standard error 0.3 injections in the sham group and 2.7 standard error 0.2 injections in
37 the aflibercept group); after the first year, patients continued in a one-year extension phase with as
38 needed dosing. In the GALILEO trial (2012)^{36;37}, intervention patients also received intravitreal
39 injections of 2 mg of aflibercept (n=103) every 4 weeks over 24 weeks, while the comparison group
40 was given sham injections (n=71). During weeks 24 to 52, patients remained in their original
41 treatment groups but received their allocated treatment as needed; beginning from week 52 to
42 week 76, both groups received the study drug every 8 weeks.
43
44
45
46
47
48
49
50

51
52 In a trial by Wroblewski and colleagues (2009)³⁸⁻⁴⁴, patients received 0.3 or 1 mg intravitreal
53 injections of pegaptanib sodium every 6 weeks for 24 weeks (n=33 and 33), compared with a sham
54 injection group (n=32). Patients were followed up to 52 weeks.
55
56
57
58
59
60

1
2
3 The CRUISE trial (2010 ff.)^{10;45;46} compared monthly injections of 0.3 or 0.5 mg of ranibizumab (n=132
4 and 130) over 6 months with sham injection (n=130). During months 6 to 12, all patients could
5 receive intraocular ranibizumab (previously assigned dose or 0.5 mg for the sham group) if they met
6 prespecified functional and anatomic criteria; after 12 months' follow-up patients could continue in
7 the HORIZON trial for another 12 months, where they were eligible to receive intravitreal injections
8 of 0.5 mg ranibizumab if they fulfilled prespecified criteria.
9

10
11
12
13 Epstein and colleagues (2012)⁴⁷⁻⁴⁹ conducted an RCT in which they compared patients receiving four
14 intravitreal injections of 1.25 mg of bevacizumab (n=30) over 6 months with patients receiving sham
15 injection (n=30). From 6 to 12 months, all patients received intravitreal bevacizumab injections every
16 6 weeks.
17
18
19

20
21 *Outcomes.* The primary endpoint of all but one study was the proportion with a gain of 15 or more
22 ETDRS letters. The primary endpoint of the remaining study was mean change in BCVA. Studies also
23 reported gains or losses of ETDRS letters at various cut-off points, absolute BCVA, CRT, and safety
24 parameters. The COPERNICUS, the GALILEO and the CRUISE studies also measured vision-related
25 quality of life (National Eye Institute Visual Functioning Questionnaire, NEI-VFQ).^{10;34-37;45;46} EQ5D was
26 also used in GALILEO.
27
28
29

30
31 *Ongoing studies.* Of the ongoing trials, the first (clinicaltrials.gov NCT01468844) is a 24 month
32 double-blind RCT from the USA. It set out to test the safety and effectiveness of minocycline as a
33 treatment for CRVO in around 20 patients with macular oedema secondary to CRVO. Both groups
34 received monthly intravitreal bevacizumab injections over three months (and afterwards as needed),
35 and the intervention group also received 100 mg oral minocycline twice daily over 24 months. The
36 second trial (clinicaltrials.gov NCT00566761) is an open-label RCT from Mexico in only around 10
37 patients assessing whether combined treatment with bevacizumab and triamcinolone is more
38 effective than bevacizumab alone. The combination group received 2.5 mg of bevacizumab plus 4
39 mg of triamcinolone as a first dose and then two doses of bevacizumab alone at monthly intervals,
40 while the monotherapy group received three monthly doses of 2.5 mg bevacizumab alone. Follow-
41 up will be 12 months. A third RCT from Hungary compares monthly injections of ranibizumab for
42 three months (and as needed thereafter) with Argon laser treatment in around 40 patients with
43 macular oedema secondary to CRVO. Follow-up will also be 12 months. The primary endpoint in all
44 studies is BCVA over 12 months.
45
46
47
48
49
50
51
52
53
54

55
56
57 *Risk of bias*
58
59
60

1
2
3 Details of risk of bias assessment are shown in Table 3.
4

5 Most studies (except GALILEO (2012) and Epstein 2012)^{36;37;47-49} adequately described the generation
6 of the allocation sequence, but only half the studies gave enough details to confirm adequate
7 allocation concealment. Most studies (unclear in the ROVO 2013 study)³³ used at least partial
8 masking, and most studies appeared to have had masking of outcome assessment. Intention-to-treat
9 analysis was used in all studies. Where reported separately for comparison groups, losses to follow-
10 up tended to be slightly higher for the control groups than the interventions groups (79 to 88.5%
11 follow-up in the control groups and 90 to 98% in the intervention groups). All studies appeared to
12 have been free of selective reporting. Most studies included a power analysis (not reported for the
13 CRUISE study)^{10;45;46}, but in two cases (the SCORE and the ROVO studies)¹⁹⁻³³ the numbers
14 randomised were considerably below the numbers indicated in the power calculations. As far as
15 reported, there were no significant differences between comparison groups in baseline
16 characteristics.
17
18
19
20
21
22
23
24
25
26
27

28 *Clinical effectiveness*

29
30 Detailed study results can be found in Table 2.
31

32
33 *Visual acuity.* Figure 2 shows the primary endpoint in most studies, which was the proportion of
34 participants with a gain of 15 or more ETDRS letters. As there were no significant differences in
35 visual acuity results between groups using different dosages of the given pharmacological treatment,
36 intervention groups were combined for the sake of the plot.
37
38

39
40 In the Geneva trial (2010 ff.)^{11;17;18}, treatment of macular oedema secondary to CRVO with a 0.7 mg
41 intravitreal dexamethasone implant resulted in a 0.1 letter gain in BCVA compared to a loss of 1.8 in
42 the sham group ($p < 0.001$). The difference persisted in the extension period where all patients
43 received the 0.7 mg dexamethasone implant. However, there was no significant difference in the
44 proportion of patients gaining or losing 15 letters at either 6 or 12 months (0.35 or 0.7 mg
45 dexamethasone). This may reflect the timing of peak effect at 90 days with dexamethasone.
46
47
48
49

50
51 In the SCORE trial (2009 ff.)¹⁹⁻³², patients in the triamcinolone groups lost significantly fewer ETDRS
52 letters (triamcinolone 1mg 1.2 letters loss, 4mg 1.2 letters loss and observation 12.1 letters loss)
53 over both 12 and 24 months than patients in the observation group. The proportion of patients
54 gaining 15 letters or more was also significantly larger in the intervention groups at 12 and 24
55 months (25.6% compared with 6.8% and 31% compared with 9%, respectively). The proportion of
56
57
58
59
60

1
2
3 patients receiving triamcinolone and losing 15 letters or more was smaller (25.6%) than in the
4 observation group (43.8%), but this difference was not statistically significant ($p=0.06$).
5
6

7 There was some overall improvement in BCVA in both intervention groups at 12 months in the ROVO
8 trial (2013)³³, (triamcinolone 20%, radial optic neurotomy 47% and sham 10%) however it was
9 unclear whether there were any statistically significant differences between the 4 mg triamcinolone,
10 the radial optic neurotomy, or the sham group. However, there were significantly more patients with
11 an improvement of more than or equal to 15 letters in the neurotomy group than in the sham group
12 (47% versus 10%), but no significant difference to sham after one dose of triamcinolone.
13
14
15
16

17 In both the COPERNICUS (2012)^{34;35} and GALILEO (2012)^{36;37} trials patients in the aflibercept group had
18 a significant improvement in BCVA at 6 months of 18 and 17.3 letters (compared to 4 letters loss and
19 3.3 letter gain in sham groups respectively), and this was maintained at 12 months and was
20 significantly greater than the improvements in the sham groups. This was paralleled by a significantly
21 greater proportion of patients (56.1% compared with 12.3% and 60.2% compared with 22.1%,
22 respectively) gaining 15 letters or more. Patients treated sooner after diagnosis (less than versus
23 more than two months) seemed to benefit more (in terms of proportion of patients with 15 letters
24 or more gain) in both trials.
25
26
27
28
29
30

31 The increase in mean change in BCVA with 0.3 mg pegaptanib compared with sham did not reach
32 significance at 30 weeks in the trial by Wroblewski and colleagues (2009)³⁸⁻⁴⁴, but there was a
33 greater increase in BCVA with 1 mg pegaptanib compared with sham (9.9 letter gain compare with
34 3.2 letter loss). These differences were not statistically significant at 52 weeks. There was no
35 significant difference between any of the groups in the proportion of patients gaining 15 letters or
36 more at 30 weeks, but significantly fewer patients in both dosage groups lost 15 letters or more than
37 in the sham group (6% compared with 31%).
38
39
40
41
42

43 In the CRUISE trial (2010 ff.)^{10;45;46}, mean change in BCVA was significantly increased in the
44 ranibizumab groups (no difference between doses) compared with the sham group at both 6 and 12
45 months (12.0 letters gained in the 0.5 mg group compared to 7.6 in the sham group). After the one
46 year extension with ranibizumab as needed in all groups, there was no difference between the doses
47 of ranibizumab at 24 months. The pattern was similar for the proportion of patients gaining 15
48 letters or more.
49
50
51
52

53 In the trial by Epstein and colleagues (2012)⁴⁷⁻⁴⁹, treatment with intravitreal bevacizumab, compared
54 with sham treatment significantly increased mean change in BCVA (14.1 letters gain compared to 2.0
55 letters lost) and the proportion of patients gaining 15 letters or more (60% compared to 20%) at 24
56
57
58
59
60

1
2
3 weeks. This difference was maintained in the extension period, even though both groups had been
4 receiving bevacizumab. Younger patients (<70 years) tended to have better visual outcomes than
5 older patients (>70 years).
6
7

8
9 *Central retinal thickness.* In the Geneva trial (2010 ff.)^{11;17;18}, no significant difference was found in
10 the reduction of CRT after 6 months' treatment in patients with macular oedema secondary to CRVO
11 with the 0.7 mg intravitreal dexamethasone implant (no data given for the 0.35 mg implant)
12 compared with sham.
13
14

15
16 In the SCORE trial (2009 ff.)¹⁹⁻³², CRT decreased in all study groups, but there was no significant
17 difference between groups at either 12 or 24 months. Similarly, there was no clear difference in the
18 proportion of patients achieving a CRT of less than 250 µm. CRT decreased in all comparison groups
19 in the ROVO trial (2013)³³, but there was no significant difference between groups.
20
21

22
23 Both in the COPERNICUS trial (2012)^{34;35} and in the GALILEO trial (2012)^{36;37} there was a significantly
24 greater reduction in CRT at 6 months in the aflibercept group than in the control group. However the
25 significant difference was maintained in the longer term only in the GALILEO trial, where patients
26 continued their assigned treatment up to 12 months. In the COPERNICUS trial, patients in the sham
27 group also received aflibercept in the extension period, which caused a similar decrease in CRT as in
28 the original intervention group.
29
30
31

32
33
34 After 30 weeks of treatment with pegaptanib (Wroblewski and colleagues 2009)³⁸⁻⁴⁴, differences in
35 decrease of CRT versus sham did not reach significance, but at 52 weeks, the decrease in CRT was
36 significantly greater in both the 0.3 mg and the 1 mg pegaptanib groups compared with sham.
37
38

39
40 After treatment with ranibizumab in the CRUISE trial (2010 ff.)^{10;45;46}, a significant reduction in CRT
41 was observed and significantly more patients achieved a CRT of 250 µm or less in the intervention
42 groups (no difference between doses) than in the sham group at 6 months. This difference did not
43 persist at 12 and 24 months because all groups received ranibizumab as needed.
44
45

46
47 In the trial by Epstein and colleagues (2012)⁴⁷⁻⁴⁹, treatment with intravitreal bevacizumab
48 significantly decreased CRT and the proportion of patients with no residual oedema (CRT <300 µm)
49 at 24 weeks, compared with sham treatment. When both groups received bevacizumab in the
50 extension period, similar decreases in CRT and increases in the proportion of patients with no
51 residual oedema were seen.
52
53
54

55
56 *Vision-related quality of life.* Vision-related quality of life (NEI-VFQ25) was significantly higher in the
57 aflibercept group, compared with sham injection, at 6 months in both the COPERNICUS trial (+7.2
58
59
60

1
2
3 compared with +0.8)^{34;35} and the GALILEO trial (+7.5 compared with +3.5)^{36;37}. In the COPERNICUS
4 trial, patients in the sham group who received aflibercept in the extension period had a similar
5 increase in vision-related quality of life as patients in the original intervention group by 12 months.
6
7

8
9 In the CRUISE trial (2010 ff.)^{10;45;46}, vision-related quality of life (NEI-VFQ) was similarly increased in
10 both ranibizumab groups and statistically significantly more than in the sham group at 6 months
11 (+6.2 compared with +2.8). At 12 months, with all groups receiving ranibizumab as needed, the
12 increases were similar in all three groups.
13
14

15
16 *Adverse events.* The 0.7 mg dexamethasone intravitreal implant caused significantly more increased
17 intraocular pressure (IOP) than sham treatment (30.1%, versus 1.4% in the control group) in patients
18 with CRVO in the Geneva trial (2010 ff.)^{11;17;18} (not reported for 0.35 mg). The incidence of cataract
19 was also slightly higher in the dexamethasone group but numbers were small because of the short
20 duration . There were no other differences in adverse events between groups.
21
22
23

24
25 In the triamcinolone group (especially 4 mg, SCORE trial 2009 ff.)¹⁹⁻³², there was a higher increase in
26 IOP, lens opacity onset or progression (at 12 months) and cataract surgery (12 to 24 months) than in
27 the control group. There were no other differences in adverse events between groups. A similar
28 tendency was seen in the ROVO trial (2013)³³.
29
30
31

32 Aflibercept did not appear to increase the incidence of ocular or non-ocular adverse events
33 compared with sham in both the COPERNICUS trial (2012)^{34;35} and the GALILEO trial (2012)^{36;37}.
34
35

36 In the trial by Wroblewski and colleagues (2009)³⁸⁻⁴⁴, adverse events in response to pegaptanib were
37 not reported in detail, but there do not appear to have been any serious ocular or systemic adverse
38 events.
39
40

41
42 After treatment with ranibizumab in the CRUISE trial (2010 ff.)^{10;45;46}, there were no consistent
43 differences in ocular or systemic adverse events between the intervention groups. None of the
44 ocular adverse events appeared to have increased substantially after all patients received
45 ranibizumab up to 24 months.
46
47

48
49 Epstein and colleagues (2012)⁴⁷⁻⁴⁹ did not report adverse events in response to bevacizumab in
50 detail, but the treatment appears not to have caused any serious ocular adverse events over 48
51 weeks.
52
53
54
55
56
57
58
59
60

Discussion

Statement of principal findings

Evidence from good quality RCTs shows that intravitreal steroids and anti-VEGF therapies increase the proportion of patients whose vision improves by 15 or more letters in patients with macular oedema secondary to CRVO. The most effective drugs result in over 60% of patients gaining 15 letters compared to only about 20% of the control groups. The RCT evidence shows only short-term effectiveness of ranibizumab, bevacizumab, aflibercept and triamcinolone. Results from trials of dexamethasone and pegaptanib were mixed. Long-term evidence is awaited.

Strengths and limitations

A robust systematic review methodology was used. A broad search strategy was implemented, which included not restricting the search strategy with drug terms. Grey literature was searched by screening meeting abstracts from relevant conferences. There were no language restrictions. Two reviewers screened titles and abstracts and conducted data extraction and risk of bias assessment. Risk of bias was assessed using the Cochrane Risk of Bias Tool and was generally judged to be low or unclear. Only studies with one year follow up were included to exclude studies with very short follow-up RCTs were identified for all the new ophthalmological drugs, except for the steroid, fluocinolone.

The main limitation is the short duration of follow-up. The primary outcome for most trials was measured at 6 months, with an extension phase up to 12 months. Hence, it is not known whether the benefit of these treatments will be maintained long-term. Furthermore, potential side effects of these treatments may not be captured in these studies as a result of their short follow-up. Patients and clinicians would like sustained, life-long improvement in visual acuity, but of all included studies only one of them had a follow-up of over 24 months.

The sample size of some studies was small. For example, the evidence for pegaptanib and bevacizumab comes from studies with around 30 participants per arm which substantially increases the risk of a type II error. Only three trials included quality of life data, arguably one of the most important outcomes.

The proportion of participants and severity of ischemia within the trials was not clear. Whilst ischaemia is not mentioned in the inclusion/exclusion criteria of most studies, these participants

1
2
3 were unlikely included in these studies, especially if the diagnosis of ischaemic CRVO is based on
4 strict criteria. Furthermore patients were entered into the trials relatively soon after diagnosis (mean
5 4.3 to 4.9 months) and the it is not clear if the effects would be similar in patients who present with
6 long standing disease.
7
8

9
10 Another weakness was that patients were not asked at the of trials, what treatment they thought
11 they had received, which would have provided data on the success of masking of allocation.
12
13

14 In the case of dexamethasone, the results at six months were not as good as at 90 days, because of
15 the duration of action. Earlier re-treatment, at say 120 days, would have improved results, but many
16 clinicians might be reluctant to repeat injections of dexamethasone implant often because of the
17 large needle size and risk of adverse effects.
18
19

20 21 *Adverse events* 22

23
24 Results from the included studies clearly demonstrate that steroids (triamcinolone and
25 dexamethasone) are associated with clinically meaningful increases in IOP and cataract progression.
26 Anti-VEGF therapy ocular adverse events reported in the trials were similar in both placebo and
27 intervention arms.
28
29

30
31 There is limited evidence of the safety of these drugs specifically in CRVO, but it would not be
32 unreasonable to look to trials in neovascular age-related macular degeneration (AMD) and diabetic
33 macular oedema (DMO) for safety data, where there is more experience. The CATT trial, which
34 compared bevacizumab with ranibizumab in AMD, suggested that there was a higher incidence (RR
35 1.29 95%CI 1.01 to 1.66) of serious systematic adverse events (primarily hospitalisations) in the
36 bevacizumab arm.⁵⁰ Some have raised concerns about arterial thromboembolic events with
37 bevacizumab, but none of these has been demonstrated in the published literature.⁵¹⁻⁵⁴ Micieli and
38 colleagues (2010) undertook a systematic review of the adverse events associated with
39 bevacizumab. 22 studies were reviewed, representing 12,699 participants.⁵⁵ Adverse events in
40 patients treated with bevacizumab were cerebrovascular events (0.21%), myocardial infarction
41 (0.19%) and increased blood pressure (0.46%). Most of these represent the background burden of
42 disease in patients with advanced eye disease. The proportion of these directly attributable to
43 bevacizumab is likely to be very small. Campbell and colleagues (2012) undertook a nested case-
44 control study of over 7,000 cases and 37,000 controls.⁵¹ Ranibizumab and bevacizumab injection was
45 the exposure and cardiovascular events were the outcome. The authors found that ranibizumab and
46 bevacizumab were not associated with increased cardiovascular events.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Increased IOP has been associated with ranibizumab, bevacizumab and pegaptanib. Sustained
4 increased in IOP has estimated to be 5.5-6.0% with these drugs.^{56;57}
5
6

7 Robust evidence on the long-term safety of aflibercept is awaited.
8
9

10 11 12 *What do these results mean?* 13

14 Until very recently, patients with macular oedema as a result of CRVO could only be offered visual
15 rehabilitation and visual aids in an attempt to help them to deal better with their reduced vision and
16 its implications in their daily activities and quality of life. Their future is brighter now as new options
17 to treat macular oedema have become available. Triamcinolone is likely to be a cost-effective
18 treatment at least in selected groups of patients, such as pseudophakic individuals or those with pre-
19 existing cataracts that may require cataract surgery in the near future. The lack of a commercially
20 available licensed product for intraocular administration may restrict its use in clinical practice.
21
22
23
24

25
26 Some anti-VEGF therapies, including bevacizumab, ranibizumab and aflibercept, have been also
27 shown to be effective in short term studies for the treatment of patients with macular oedema and
28 CRVO. Bevacizumab has the advantage of having a low cost , with an apparently similar effect to
29 other anti-VEGF therapies^{50;58;59} but there is some reluctance to use it as it is not licensed for use in
30 the eye. This has been seen in other eye conditions, such as AMD and DMO. Aflibercept, requiring
31 potentially fewer injections than other anti-VEGF agents, could represent an advantage to patients
32 and may relieve pressure on ophthalmology clinics. Health care systems will need to evaluate the
33 cost-effectiveness of these new treatments and support affordable ones. The National Institute for
34 Health and Care Excellence is currently appraising aflibercept. Policy makers are left in a difficult
35 position because of bevacizumab. It is cheaper than all other drugs⁶⁰ and appears to be as effective,
36 but is unlicensed and unlike ranibizumab and aflibercept does not have evidence from large, well-
37 funded RCTs in CRVO. The use of bevacizumab would result in considerable savings for the NHS.
38
39
40
41
42
43
44
45

46 It is important to note that the evidence of benefit of these new therapies is likely to only apply to
47 patients with non-ischaemic CRVO. Although some patients with ischaemic CRVO were included,
48 these individuals are likely to have mild ischaemic CRVO. Thus, for patients with established
49 ischaemic CRVO, there are no proven treatments available and further research into this area is very
50 much needed.
51
52
53
54
55

56 57 58 *What is the context of these results* 59 60

1
2
3 Earlier systematic reviews identified limited evidence on the clinical effectiveness of treatments. A
4 review by Braithwaite and colleagues (search date August 2010)⁶¹ on anti-VEGF agents identified one
5 RCT^{10;45;46} comparing two doses of ranibizumab and one RCT³⁸⁻⁴⁴ comparing two doses of pegaptanib
6 sodium versus placebo or no treatment. In both RCTs, the higher dose of the anti-VEGF significantly
7 improved BCVA compared with sham injection in the short term (~6 months), but the effects in the
8 longer term were unclear. Braithwaite and colleagues concluded that data from the two RCTs could
9 not be synthesised because ranibizumab and pegaptanib sodium might not be directly comparable.
10 Subsequent RCTs identified in this review also suggest benefit in ocular outcomes in macular
11 oedema secondary to non-ischaemic CRVO for the anti-VEGFs bevacizumab, and aflibercept.^{34-37;47-49}

12
13
14
15
16
17
18 Gewaily and Greenberg reviewed the literature on intravitreal corticosteroids (search date
19 November 2008) versus observation in macular oedema secondary to CRVO and identified no
20 relevant RCTs.⁶² Results from two observational studies suggested that triamcinolone acetonide
21 might be beneficial in the treatment of macular oedema secondary to non-ischaemic CRVO.
22 However, as the authors of the review caution because conclusions are primarily drawn from small
23 case series and case reports with short follow up. Results from the SCORE 2009 RCT corroborate the
24 observational studies.¹⁹⁻³² The effects of triamcinolone acetonide in people with non-ischaemic CRVO
25 without associated macular oedema are less clear. Data from four observational studies led Gewaily
26 and Greenberg to conclude that intravitreal corticosteroids are associated with transient anatomical
27 and functional improvements.

28
29
30
31
32
33
34
35 Immediate treatment aimed at relieving the blocked vein and surgical interventions were outwith
36 the remit of this review. Antithrombotics, such as low-molecular weight heparin (LMWH), and
37 fibrinolytics have also been found to benefit visual acuity in retinal vein occlusion with no associated
38 macular oedema. Two systematic reviews^{63;64} identifying the same three RCTs in recent onset (≤ 30
39 days) BRVO or CRVO found that LMWH improved visual acuity compared with aspirin and that the
40 associated benefit was larger in CRVO; only one of the three RCTs included people solely with CRVO.
41 One review⁶⁴ also included one RCT comparing ticlopidine with placebo and two RCTs assessing
42 intravenous fibrinolytic therapy followed by warfarin or aspirin with either haemodilution or no
43 treatment. The authors of the reviews conclude that no definitive recommendations can be made on
44 clinical effectiveness of LMWH in CRVO given the limited evidence available.

45
46
47
48
49
50
51
52 Radial optic neurotomy involves the performance of a radial cut using a microvitrectomy (MVR)
53 blade through the lamina cribrosa, scleral ring and adjacent sclera at a selected point in the optic
54 nerve head with the goal of "decompressing" the scleral outlet (space confined by the scleral ring
55
56
57
58
59
60

1
2
3 and containing the lamina cribrosa, the central retinal artery, central retinal vein and the optic
4 nerve. The ROVO trial found radial optic neurotomy to be more effective than sham.
5
6

7 While this review was being considered for publication, another was published, with differences in
8 scope (BRVO and CRVO) and inclusions (this review is more up to date).⁶⁵ The reviewers found that
9 aflibercept and bevacizumab resulted in greatest gain, followed by ranibizumab and triamcinolone.
10 The overall conclusions in both reviews were similar.
11
12

13 *Further research*

14
15
16 Large adequately powered RCTs comparing ranibizumab, bevacizumab, aflibercept and
17 triamcinolone are needed. Part of the problem is that the US the Food and Drug Administration
18 requires pharmaceutical companies to present data establishing a drug's safety and effectiveness.
19 Whilst this does not specifically require a placebo-controlled trial, it is the most efficient study
20 design for demonstrating effectiveness and safety. Clinicians and researchers are left with placebo-
21 controlled trials demonstrating effectiveness for individual drugs, but a lack of evidence to help
22 them decide which is best for their patients.
23
24
25
26
27

28
29 Given the cost of these treatments and the burden of repeated injections to patients and health care
30 systems, research aiming to predict "responders" would be useful as at present this is done by
31 therapeutic trial. Treatments could then be targeted to patients likely to benefit. Research is also
32 needed on the frequency and sequences of drugs. As other pathogenic pathways besides
33 inflammation and VEGF-mediated pathways may be implicated in the development of macular
34 oedema in patients with CRVO, these should be investigated in an attempt to develop new
35 therapeutic strategies for this condition. Research is also needed into optimum timing of treatment
36 after CRVO. The cost-effectiveness of diagnostic technologies for determining when retreatment is
37 necessary should be examined.
38
39
40
41
42

43
44 We also need better treatments since a significant proportion of patients do not improve with all of
45 these drugs
46
47

48 Future RCTs should include longer term outcomes, as functional results observed at six months or
49 even one year may not necessarily be representative of what is likely to be achieved longer term
50 and, furthermore, potential side effects of treatments, such as retinal atrophy after repeated
51 injections of anti-VEGFs, may not be captured in shorter term studies.
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Conclusions

Bevacizumab, ranibizumab, aflibercept and triamcinolone appear to be effective in improving the number of patients who gain 15 letters or more in CRVO. There are mixed results for dexamethasone and pegaptanib. Steroids were associated with cataract progression and increased IOP. Long-term data on effectiveness and safety are needed. Head-to-head trials and research to identify “responders” is needed to help clinicians make the right choices for their patients.

For peer review only

1
2
3 Figure legends
4

5 Figure 1: PRISMA statement
6
7

8 Figure 2. **Study results for the primary outcome (≥ 15 ETDRS letter gain).**
9
10
11
12
13

14
15 **Acknowledgments:** None
16

17 **Conflict of interest:** None
18

19 **Funding:** This research received no specific grant from any funding agency in the public, commercial
20 or not-for-profit sectors
21

22 **Contributions:** NW devised the idea for the review. JF wrote the protocol and all authors
23 contributed to the design of the protocol. RC undertook the literature searches. JF, CC and ST
24 screened titles and abstracts. CC, ST and DS extracted the data. All authors contributed to the
25 interpretation of the results. JF, NL, RC, CC and SB contributed to the first draft of the article. All
26 authors reviewed and commented on the final manuscript.
27
28
29
30

31 Data sharing: No additional data available
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 Table 1: Study characteristics

Study	Participants and baseline values	Intervention / Outcomes
DEXAMETHASONE		
<p>GENEVA 2010 ff.^{11;17;18}</p> <p>International</p> <p>Setting: multicentre (167 centres in 24 countries, so a mean of 2.6 patients per centre)</p> <p>Study aim: to evaluate the effects of dexamethasone intravitreal implant in patients with macular oedema secondary to CRVO or BRVO (only data for CRVO reported here)</p> <p>Design: 2 identical double-blind, sham-controlled RCTs, phase 3</p> <p>Follow-up: primary endpoint for the masked trial: 6 months; primary endpoint for the open-label extension: 12 months</p> <p>Overall quality: 5.5/6</p>	<p>N: CRVO – 437 eyes of 437 patients randomised; 94% follow-up at 6 months</p> <p>Inclusion criteria: ≥18 years; reduced VA due to macular oedema due to CRVO or BRVO which in the investigator’s opinion, is unlikely to be adversely affected if not treated for 6 months; duration of macular oedema 6 weeks to 9 months in patients with CRVO; BCVA 34 to 68 ETDRS letters (~20/200 and 20/50 Snellen equivalent) in the study eye and >34 letters in the non-study eye; CRT ≥300 µm (OCT)</p> <p>Exclusion criteria: <i>study eye:</i> clinically significant epiretinal membrane; use of periocular corticosteroid within 6 months or topical nonsteroidal anti-inflammatory drug or corticosteroid within 1 month; intraocular surgery or laser within 30 days of study or anticipated; history of intravitreal use of corticosteroid or any other drug; glaucoma; IOP >23 mmHg if untreated or >21 if treated with one medication; treatment with ≥2 IOP-lowering medications; active retinal, optic disc or choroidal neovascularisation; history of herpetic infection; rubeosis iridis, aphakia or anterior-chamber intraocular lens; any ocular condition that would prevent a 15-letter VA improvement; preretinal or vitreous haemorrhage, lens opacity, media opacity that would preclude clinical or photographic evaluation; history of pars plana vitrectomy; <i>any eye:</i></p>	<p>DEX 0.7 (n=136): sustained delivery, biodegradable dexamethasone intravitreal implant (Ozurdex), 0.7 mg implant inserted into the vitreous cavity through the pars plana using a customised, single-use, 22-gauge applicator</p> <p>DEX 0.35 (n=154): DEX 0.35 mg implant inserted following the same method</p> <p>Sham (n=147): a needleless applicator was placed against the conjunctiva to simulate the placement of study medication.</p> <p>Regimen for all groups: before inserting the implant, the study eye was anaesthetised with topical and subconjunctival anaesthetics and prepared according to standard clinical practice for eyes undergoing intravitreal injection; patients were treated with a topical ophthalmic antibiotic 4 times daily starting 3 days before the day of their study procedure (day 0) and continuing for 3 days after the procedure</p> <p>Extension: patients completing 180 days were eligible to enter a 6 month open label extension where they received DEX 0.7 mg implant</p> <p>Primary end point: gain of ≥15 ETDRS letters; for the open-label extension: safety</p>

Study	Participants and baseline values	Intervention / Outcomes
	<p>active ocular infection; history of steroid-induced IOP–increase; diabetic retinopathy; <i>other</i>: uncontrolled systemic disease; current or anticipated use of systemic steroids or anticoagulants</p> <p>Age (years): 62.7 to 65.2 years</p> <p>Sex: 43.7 to 49.2% (CRVO and BRVO together)</p> <p>Baseline VA (ETDRS letters):52.4 SD10.6</p> <p>Baseline CRT (µm):DEX 0.7: 648; Sham: 620</p> <p>Other ocular information: phakic status (%): 85 to 88%</p> <p>Duration of macular oedema: mean 4.8 to 4.9 months;<90 days: 14.3 to 15.4%; >90 to <180 days: 54.4 to 57.4%, >180 days: 27.1 to 31.3%</p> <p>Comorbidities: diabetes mellitus 14 to 15%, hypertension 62 to 64%, coronary artery disease 9 to 13%, IOP-lowering medication at baseline 4 to 6% (all for CRVO and BRVO together)</p>	<p>Other outcomes: proportion of eyes achieving at least a 10 and 15 letter improvement from baseline; the proportion of eye exhibiting ≥15 letters of worsening; BCVA; subgroup analysis according to RVO diagnosis (BRVO and CRVO) and duration of macular oedema at baseline; CRT and safety</p> <p>Outcome assessment: evaluation at 1, 7, 30, 60, 90 and 180 days after study treatment for both parts of the study</p>
TRIAMCINOLONE		
<p>SCORE 2009 ff.¹⁹⁻³²</p> <p>USA</p> <p>Setting: multicentre</p> <p>Study aim: to compare the effects of 1 and 4 mg preservative-free</p>	<p>N: 271 eyes of 271 patients randomised; 83% (observation) and 90% (intervention) completed 12 months</p> <p>Inclusion criteria: centre-involved macular oedema secondary to CRVO, BCVA 19 to 73 ETDRS letters (Snellen equivalent ~20/400 to 20/40), CRT >250 µm by OCT; media clarity, papillary dilatation and participant</p>	<p>Tria (1 mg) (n=92): 1 mg (0.05 ml) of preservative-free, nondispersive formulation of triamcinolone (average number of injections 2.2 at 12 months)</p> <p>Tria (4 mg) (n=91): 4 mg (0.05 ml) of preservative-free, nondispersive formulation of triamcinolone(average number of injections 2.0 at 12 months)</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Participants and baseline values	Intervention / Outcomes
<p>intravitreal triamcinolone with observation in eyes with vision loss associated with macular oedema secondary to perfused CRVO</p> <p>Design: RCT</p> <p>Follow-up: primary end point 12 months, FU planned up to 36 months</p> <p>Overall quality: 3/6</p>	<p>cooperation sufficient for adequate fundus photographs</p> <p>Exclusion criteria: macular oedema due to causes other than CRVO, ocular condition such that visual acuity would not improve from resolution of oedema, substantial cataract, prior treatment with intravitreal corticosteroids or peribulbar steroid injection within 6 months, photocoagulation (prior 4 months or anticipated), prior pars plana vitrectomy, major ocular surgery (prior 6 months or anticipated), IOP \geq25 mmHg, open-angle glaucoma, steroid-induced IOP-elevation requiring IOP-lowering treatment, pseudoexfoliation, aphakia</p> <p>Age: 68.0 SD 12.4 years</p> <p>Sex: 45% female</p> <p>Duration of macular oedema: 4.3 SD3.7 months</p> <p>Baseline VA (ETDRS letters): 51.2 SD14.1</p> <p>Baseline CRT (μm): 659 SD229</p> <p>Other ocular information: 81% phakic, IOP 15.5 SD3.2 mmHg</p> <p>Comorbidities: 23% diabetes mellitus, 73% hypertension, 21% coronary artery disease, 21% history of cancer</p>	<p>The form of triamcinolone used was Trivaris, no longer available. It was made by the manufacturer of Ozurdex (Allergan)</p> <p>Obs (n=88): observation</p> <p>Regimen for all groups: all intervention eyes received standardised ocular surface preparation prior to injection (eyelid speculum, topical anaesthetic, topical antibiotics, asepsis with povidone iodine); retreatment every 4 months unless (1) treatment was deemed successful (defined), (2) treatment was contraindicated because of significant adverse effect, (3) additional treatment was considered 'apparently futile' (defined)</p> <p>Primary end point: gain of \geq15 ETDRS letters</p> <p>Other outcomes: BCVA, intraocular pressure, eye examination including dilated fundus examination, OCT scan for thickness, , lens opacities, , adverse events</p> <p>Outcome assessment: follow-up visits every 4 months for 36 months</p>
<p>ROVO 2013³³</p>	<p>N: 90 patients randomised; 82% evaluated</p> <p>Inclusion criteria: history of CRVO not longer than 12</p>	<p>Tria (n=25): single intravitreal injection of 4 mg triamcinolone acetonide (100 μl) applied after povidone</p>

Study	Participants and baseline values	Intervention / Outcomes
<p>Austria</p> <p>Setting: multicentre (7 centres in 7 countries)</p> <p>Study aim: to compare the effects of radial optical neurotomy with intravenous triamcinolone and natural history (placebo) in patients with CRVO</p> <p>Design: RCT, placebo-controlled</p> <p>Follow-up: primary end point 12 months</p> <p>Overall quality: 3.5/6</p>	<p>months; VA of ≥ 0.3 logMAR (≤ 85 letters) (for perfused CRVO: VA > 1 logMAR (> 50 letters) or no VA improvement over 4 weeks)</p> <p>Exclusion criteria: dense cataract, severe ophthalmologic conditions (severe retinopathy, presence of advanced optic atrophy, uncontrolled glaucoma), pregnancy, allergy against fluoresceine or indocyanine green, any handicap which could prevent patients from attending follow-up visits</p> <p>Age: not reported</p> <p>Sex: 36% female</p> <p>Duration of macular oedema: not reported</p> <p>Baseline VA (ETDRS letters) : 1.07 logMAR (interquartile range 0.78 to 1.7) (~46 letters)</p> <p>Baseline CRT (μm): 569 to 657 μm</p> <p>Other ocular information: not reported</p> <p>Comorbidities: 23% diabetes mellitus, 49% hypertension, 17% cardiovascular disease, 4% hypercoagulopathies, 1% leukaemia, 2% anaemia</p>	<p>iodine drops; postoperative topical antibiotics</p> <p>RON (n=38): radial optical neurotomy under general anaesthesia (detailed procedure described)</p> <p>Pla (n=20): eyes prepared as for triamcinolone injection but sham injection performed (empty syringe without needle pressed against the eye)</p> <p>Primary end point: gain of ≥ 15 ETDRS letters</p> <p>Other outcomes: BCVA, CRT, safety</p> <p>Outcome assessment: 12 months</p>
AFLIBERCEPT		
<p>COPERNICUS 2012^{34;35}</p> <p>International</p>	<p>N: 189 eyes of 189 patients randomised; 95.7% (aflibercept) and 81.1% (sham) completed 24 weeks; 93% (aflibercept) and 77% (sham) completed 52 weeks</p>	<p>VTE (n=114): intravitreal injections of 2 mg aflibercept (50 μl) every 4 weeks for 24 weeks</p> <p>Sham (n=73): sham procedure (empty syringe without</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Participants and baseline values	Intervention / Outcomes
<p>Setting: multicentre, 70 sites in North and South America, India and Israel. Mean 2.7 patients per centre.</p> <p>Study aim: to evaluate the effects of intravitreal aflibercept in patients with macular oedema secondary to CRVO</p> <p>Design: double-blind, sham-controlled RCT, phase 3</p> <p>Follow-up: primary end point 24 weeks, FU 2 years</p> <p>Overall quality: 5/6</p>	<p>Inclusion criteria: adult patients with centre-involved CRVO for a maximum of 9 months, CRT $\geq 250 \mu\text{m}$ with OCT, ETDRS BCVA of 73 to 24 letters (Snellen equivalent 20/40 to 20/320)</p> <p>Exclusion criteria: history of vitreoretinal surgery (incl. radial optic neurotomy or sheathotomy); current bilateral retinal vein occlusion; previous pan-retinal or macular laser photocoagulation; other reasons for decreased visual acuity; ocular conditions with poorer prognosis in the fellow eye; history or presence of age-related macular degeneration, diabetic macular oedema, or diabetic retinopathy; any use of intraocular or periocular corticosteroids or antiangiogenic treatment in the study eye at any time or in the fellow eye in the preceding 3 months; iris neovascularisation, vitreous haemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula; vitreomacular traction or epiretinal membrane significantly affecting central vision; ocular inflammation; uveitis; any intraocular surgery in the preceding 3 months; aphakia; uncontrolled glaucoma, hypertension, or diabetes; spherical equivalent of a refractive error of more than -8 diopters; myopia; infectious blepharitis, keratitis, scleritis, or conjunctivitis; cerebral vascular accident or myocardial infarction in the preceding 6 months; and other conditions that could interfere with interpretation of the results or increase the risk of complications; cataract surgery was not allowed during the 3 months before randomisation.</p>	<p>needle pressed to conjunctival surface) every 4 weeks for 24 weeks</p> <p>Regimen for all groups: all patients eligible to receive pan-retinal photocoagulation for neovascularisation at any time at the discretion of the investigator; patients were not allowed to use other systemic or local medications for treating CRVO in the study eye over the first 52 weeks of the study; a noninvestigational therapy could be used to treat CRVO in the fellow eye</p> <p>Extension: during weeks 24 to 52, patients in both groups were evaluated monthly and received aflibercept if they met protocol-specified retreatment criteria, and received a sham injection if retreatment was not indicated (3.9 SE0.3 injections in the sham group and 2.7 SE0.2 injections in the VTE group); after the first year, patients continued in a 1 year extension phase with as needed dosing</p> <p>Primary end point: gain of ≥ 15 ETDRS letters</p> <p>Other outcomes: BCVA, CRT, proportion of patients progressing to neovascularisation of the anterior segment, optic disc or elsewhere in the retina, changes in vision-related quality of life (National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), safety</p> <p>Outcome assessment: examination every 4 weeks up to 24 weeks, 52 weeks</p>

Study	Participants and baseline values	Intervention / Outcomes
	<p>Age: 66.3 SD 13.9 years</p> <p>Sex: 43% female</p> <p>Time since CRVO diagnosis: 2.4 SD2.8 months; 62.0% ≤2 months, 37.4% >2 months</p> <p>Baseline VA (ETDRS letters) : 50.0 SD14.1 ; 75.4% >20/200</p> <p>Baseline CRT (µm): 665.8 SD239.8</p> <p>Other ocular information: 67.9% perfused retinal occlusion, IOP 15.1 SD3.08 mmHg</p> <p>Comorbidities: not reported</p>	
<p>GALILEO 2012^{36,37}</p> <p>International</p> <p>Setting: multicentre, 10 countries in Europe and Asia; 63 centres in total</p> <p>Study aim: to evaluate the effects of intravitreal aflibercept in patients with macular oedema secondary to CRVO</p> <p>Design: double-blind, sham-controlled RCT, phase 3</p> <p>Follow-up: primary end point 24 weeks, FU up to 12 months, planned</p>	<p>N: 177 eyes of 177 patients randomised; 90.6% (aflibercept) and 78.9% (sham) completed 24 weeks</p> <p>Inclusion criteria: treatment-naïve patients, age ≥18 years, centre-involved CRVO for a maximum of 9 months, CRT ≥250 µm with OCT, ETDRS BCVA of 73 to 24 letters (Snellen equivalent 20/40 to 20/320)</p> <p>Exclusion criteria: uncontrolled glaucoma (IOP≥25 mmHg), filtration surgery, bilateral manifestation of retinal vein occlusion, iris neovascularisation, previous treatment with anti-VEGF agents, pan-retinal or macular laser photocoagulation, intraocular corticosteroids, pregnant</p> <p>Age: 61.5 SD 12.9 years</p>	<p>VTE (n=103): intravitreal injections of 2 mg aflibercept every 4 weeks for 24 weeks</p> <p>Sham (n=71): sham procedure (empty syringe without needle pressed to conjunctival surface) every 4 weeks for 24 weeks</p> <p>Regimen for all groups: pan-retinal photocoagulation allowed at any time for all patients if they progressed to neovascularisation of the anterior segment, optic disc or fundus</p> <p>Extension: during weeks 24 to 52, patients remained in their original treatment groups but received their allocated treatment as needed; beginning from week 52 to week 76 both groups received treatment every 8</p>

Study	Participants and baseline values	Intervention / Outcomes
<p>up to 76 weeks</p> <p>Overall quality: 4/6</p>	<p>Sex: 44.4% female</p> <p>Time since CRVO diagnosis: 81.8 SD85.4 days; 52.6% <2 months, 46.2% ≥2 months, 1.2% missing</p> <p>Baseline VA (ETDRS letters) : 52.2 SD15.7, 83% >20/200</p> <p>Baseline CRT (μm): 665.5 SD231.0</p> <p>Other ocular information: 83.6% perfused retinal occlusion, IOP 14.9 SD2.7 mmHg</p> <p>Comorbidities: Renal impairment: 31% mild, 8.2% moderate, 1.2% severe; 2.9% hepatic impairment</p>	<p>weeks</p> <p>Primary end point: gain of ≥15 ETDRS letters</p> <p>Other outcomes: BCVA, CRT, proportion of patients progressing to neovascularisation of the anterior segment, optic disc or elsewhere in the fundus, changes in vision-related and overall quality of life (National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), European Quality of Life-5 Dimensions (EQ-5D)), safety</p> <p>Outcome assessment: 24 weeks, 52 weeks</p>
PEGAPTANIB		
<p>Wroblewski 2009³⁸⁻⁴⁴</p> <p>International</p> <p>Number of sites: not reported</p> <p>Setting: multicentre, practitioners' offices and clinics in Australia, France, Germany, Israel, Spain, USA</p> <p>Study aim: to evaluate the effects of intravitreal pegaptanib sodium in patients with macular oedema secondary to CRVO</p> <p>Design: double-blind, sham-</p>	<p>N: 98 eyes of 98 patients randomised; 93% completed 30 weeks</p> <p>Inclusion criteria: age ≥18 years, CRVO with onset within 6 months prior to baseline, CRT ≥250 μm with OCT, ETDRS BCVA of 65 to 20 letters (Snellen equivalent 20/50 to 20/400) and better than 35 letters (20/200) in the fellow eye</p> <p>Exclusion criteria: subtenon corticosteroid administration for any ophthalmic condition; prior panretinal or sector scatter photocoagulation; signs of old branch retinal vein occlusion or CRVO in the study eye; any other retinal vascular disease including diabetic retinopathy; eyes with a brisk afferent pupillary defect;</p>	<p>PS 0.3 mg (n=33): intravitreal injections of 0.3 mg pegaptanib sodium every 6 weeks for 24 weeks (5 injections)</p> <p>PS 1 mg (n=33): intravitreal injections of 1 mg pegaptanib sodium every 6 weeks for 24 weeks (5 injections)</p> <p>Sham (n=32): sham procedure (blunt pressure applied to the globe without a needle) every 6 weeks for 24 weeks</p> <p>Regimen for all groups: antiseptic procedures were the same for all participants (including those receiving sham); all participants received injected subconjunctival anaesthetic; panretinal photocoagulation permitted at</p>

Study	Participants and baseline values	Intervention / Outcomes
<p>controlled RCT, phase 2</p> <p>Follow-up: primary end point 30 weeks, FU up to 12 months</p> <p>Overall quality: 6/6</p>	<p>vitreous haemorrhage except for breakthrough haemorrhage from intraretinal haemorrhage; evidence of any neovascularisation involving the iris, disc, or retina; any other clinically significant concomitant ocular diseases</p> <p>Age: 59 to 64 years</p> <p>Sex: 47% female</p> <p>Time from occlusive event to study entry: 77 to 82 days</p> <p>Baseline VA (ETDRS letters): 47.6 to 48.5 letters</p> <p>Baseline CRT (μm): 632 to 688</p> <p>Other ocular information: not reported</p> <p>Comorbidities: not reported</p>	<p>any time point for neovascularisation according to the Central Vein Occlusion Study protocol; intravitreal steroids not permitted at any time</p> <p>Extension: FU to 52 weeks</p> <p>Primary end point: gain of ≥ 15 ETDRS letters</p> <p>Other outcomes: BCVA, loss of ≥ 15 letters, CRT, proportion of eyes progressing to retinal or iris neovascularisation, safety</p> <p>Outcome assessment: assessments every 6 weeks up to week 30, FU to week 52</p>
RANIBIZUMAB		
<p>CRUISE 2010 ff.^{10,45,46}</p> <p>USA</p> <p>Number of sites: not reported</p> <p>Setting: multicentre</p> <p>Study aim: to evaluate the effects of intravitreal ranibizumab (0.3 or 0.5 mg) in patients with macular oedema secondary to CRVO</p>	<p>N: 392 eyes of 392 patients randomised; 97.7% (ran 0.3 mg), 91.5% (ran 0.5 mg), and 88.5% (sham) completed 6 months</p> <p>Inclusion criteria: age ≥ 18 years, foveal centre-involved macular oedema secondary to CRVO diagnosed within 12 months before study began, CRT $\geq 250 \mu\text{m}$ with OCT, BCVA 20/40 to 20/320 (ETDRS charts)</p> <p>Exclusion criteria: prior episode of retinal vein</p>	<p>Ran 0.3 mg (n=132): intravitreal injections of 0.3 mg ranibizumab monthly for 6 months (maximum 6 injections)</p> <p>Ran 0.5 mg (n=130): intravitreal injections of 0.5 mg ranibizumab monthly for 6 months (maximum 6 injections)</p> <p>Sham (n=130): sham procedure (empty syringe without needle pressed to the injection site) monthly for 6 months</p>

Study	Participants and baseline values	Intervention / Outcomes
<p>Design: double-blind, sham-controlled RCT, phase 3</p> <p>Follow-up: primary end point 6 months, FU up to 12 months</p> <p>Overall quality: 4.5/6</p>	<p>occlusion, brisk afferent pupillary defect, >10-letter improvement in BCVA between screening and day 0, history of radial optic neurotomy or sheathotomy, intraocular corticosteroid use in study eye in prior 3 months, history or presence of wet or dry age-related macular oedema, recent or anticipated panretinal scatter photocoagulation or sector laser photocoagulation, laser photocoagulation for macular oedema in prior 4 months, evidence on examination of any diabetic retinopathy, stroke or myocardial infarction in prior 3 months, prior anti-VEGF treatment in study or fellow eye in prior 3 months or systemic anti-VEGF or pro-VEGF treatment in prior 6 months</p> <p>Age: 65.4 SD13.1 to 69.7 SD11.6 years</p> <p>Sex: 38.5 to 46.2% female</p> <p>Time since CRVO diagnosis: 2.9 SD2.9 to 3.6 SD3.2 months; 65.9 to 72.3% ≤3 months</p> <p>Baseline VA (ETDRS letters): 47.4 to 49.2 (SD 14.6 to 14.8) (range 9 to 72), 38.5 to 42.3% ≥55</p> <p>Baseline CRT (µm): 679.9 SD242.4 to 688.7 SD253.1</p> <p>Other ocular information: IOP 14.9 SD3.3 to 15.1 SD3.1 mmHg, 10.0 to 16.9% IOP-lowering medication, n=2 >10 disc areas of non-perfusion; fellow eye BCVA 78.8 SD 17.4 to 80.0 SD12.5</p>	<p>Regimen for all groups: prior to injection or sham: topical anaesthetic drops, subconjunctival injection of 2% lidocaine, cleaning of injection site with 5% povidone iodine</p> <p>Extension: months 6 to 12: all patients could receive intraocular ranibizumab (previously assigned dose or 0.5 mg for the sham group) if they met pre-specified functional and anatomic criteria (3.7 injections sham group, 3.8 injections 0.3 mg ran group, 3.3 injections 0.5 mg ran group); after 12 months' FU, 304 CRUISE patients continued in the HORIZON study for another 12 months, where patients were evaluated at least every 3 months and were eligible to receive an intravitreal injection of 0.5 mg ranibizumab if they fulfilled prespecified criteria (2.9 SD2.7 injections sham group, 3.8 SD2.8 injections 0.3 mg ran group, 3.5 SD2.7 injections 0.5 mg ran group)</p> <p>Primary end point: mean change from baseline BCVA</p> <p>Other outcomes: percentage gaining ≥15 letters, percentage losing ≥15 letters, CRT, percentage with CRT <250 µm, vision-related quality of life (National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), safety</p> <p>Outcome assessment: monthly visits up to 12 months; 3-monthly evaluation up to 24 months (HORIZON)</p>

Study	Participants and baseline values	Intervention / Outcomes
	Comorbidities: not reported	
BEVACIZUMAB		
<p data-bbox="176 428 365 457">Epstein 2012⁴⁷⁻⁴⁹</p> <p data-bbox="176 490 268 519">Sweden</p> <p data-bbox="176 607 567 669">Setting: Single centre; St. Eriks Eye Hospital Stockholm</p> <p data-bbox="176 701 596 828">Study aim: to evaluate the effects of intraocular injections of bevacizumab in patients with macular oedema secondary to CRVO</p> <p data-bbox="176 860 562 922">Design: sham-injection controlled, double masked RCT</p> <p data-bbox="176 954 575 1049">Follow-up: primary end-point 6 months; open label extension up to 12 months</p> <p data-bbox="176 1081 399 1110">Overall quality: 5/6</p>	<p data-bbox="623 428 1226 490">N: 60 eyes of 60 patients randomised; 93% completed open label extension</p> <p data-bbox="623 581 1218 675">Inclusion criteria: CRVO of ≤ 6 months; BCVA 15 to 65 ETDRS letters (Snellen equivalent $\sim 20/50$ to $20/500$), CRT $\geq 300 \mu\text{m}$ by OCT</p> <p data-bbox="623 708 1251 932">Exclusion criteria: CRVO with neovascularisation; previous treatment for CRVO; intraocular surgery during previous 3 months; vascular retinopathy of other causes; glaucoma with advanced visual field defect or uncontrolled ocular hypertension $>25 \text{ mmHg}$ despite full therapy; myocardial infarction or stroke during last 12 months</p> <p data-bbox="623 1023 886 1052">Age: 70.5 SD 12.6 years</p> <p data-bbox="623 1084 806 1114">Sex: 40% female</p> <p data-bbox="623 1146 1201 1208">Time from diagnosis to inclusion: 8.8 SD 5.7 weeks; 71.7% <90 days, 28.3% >90 days</p> <p data-bbox="623 1240 1234 1302">Baseline VA (ETDRS letters) : 44.1 SD 15.5 ; 31.7% <34, 68.3% >34</p>	<p data-bbox="1278 428 1856 490">Bev (n=30): 1.25 mg (0.05 ml) bevacizumab via pars plana</p> <p data-bbox="1278 522 1869 584">Sham (n=30): sham injection (syringe without needle pressed to the globe)</p> <p data-bbox="1278 617 1902 743">Regimen for all groups: 4 injections received, one every 6 weeks; eyes treated with topical antibiotics 30 min before injection, topical chlorhexidine, topical anaesthesia with 1% tetracaine</p> <p data-bbox="1278 776 1894 870">Open label extension: months 6 to 12, intravitreal bevacizumab injections every 6 weeks (4 injections) for all patients</p> <p data-bbox="1278 961 1780 990">Primary end point: gain of ≥ 15 ETDRS letters</p> <p data-bbox="1278 1023 1885 1149">Other outcomes: BCVA, OCT images, CRT, fluorescein angiogram, colour and red-free photography, slit-lamp examination with dilated fundus-examination, intraocular pressure, adverse events</p> <p data-bbox="1278 1182 1902 1243">Outcome assessment: follow-up visits every 6 weeks up to 24 weeks</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Participants and baseline values	Intervention / Outcomes
	<p>Baseline CRT (μm): 721 SD 269</p> <p>Comorbidities: 48.3% hypertension, 6.7% diabetes mellitus</p>	

2 **Abbreviations:** BCVA – best corrected visual acuity, CRT – central retinal thickness, CRVO – central retinal vein occlusion, ETDRS – Early Treatment Diabetic
3 Retinopathy Study, FU – follow-up, IOP – intraocular pressure, OCT – optical coherence tomography, SD – standard deviation, SE – standard error

peer review only

6 Table 2: Study results and adverse events

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events
DEXAMETHASONE		

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events					
GENEVA 2010 ff. ^{11;17;18}		Baseline	6 months	p	12 months	p	AE	DEX 0.35	DEX 0.7 (n = 133)	Sham (n = 147)	p
	BCVA (mean letters)						6 months				
	<i>DEX 0.35</i>	-	-				Overall incidence of ocular adverse events				
	<i>DEX 0.7</i>	52.4 SD 10.6	+0.1	< 0.001 vs sham	<i>DEX 0.7/0.7</i>	+2 (estimated from graph)			68.4%	49.7%	
	<i>Sham</i>	53.3 SD 10.8	-1.8		<i>Sham/DEX 0.7</i>	-1.4 (ditto)	Common Ocular Adverse Events				
	≥15 letters gained						Intraocular pressures increased		40 (30.1%)	2 (1.4%)	<0.001
	<i>DEX 0.35</i>		17%	NS vs sham			Common treatment-related Ocular Adverse Events				
	<i>DEX 0.7</i>		18.4%	NS vs sham	<i>DEX 0.7/0.7, day 240</i>	27%	IOP increased		39 (29.3%)	1 (0.7%)	<0.001
					<i>DEX 0.7 (n=19), day 360</i>	26%	Cataract adverse events				
	<i>Sham</i>		12.2%	NS vs sham	<i>Sham/DEX 0.7, day 240</i>	21%	Cataract		3 (2.3%)	2 (1.4%)	
	≥15 letters lost						Cataract subcapsular		4 (3.0%)	1 (0.7%)	
	<i>DEX 0.35</i>		-	-			Cataract nuclear		3 (2.3%)	1 (0.7%)	
	<i>DEX 0.7</i>		14.0%	NS			Cataract cortical		1 (0.8%)	3 (2.0%)	
	<i>Sham</i>		20.4%				Serious adverse events – not given separately for CRVO				
	Subgroups										
Duration of macular oedema											
>90 days	<i>DEX 0.7</i>	17.7%									
	<i>Sham</i>	9.6%									
≤90 days	<i>DEX 0.7</i>	26.0%									
	<i>Sham</i>	27.3%									

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events																																								
	<p>CRT (µm):</p> <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>6months (mean)</th> <th>p</th> <th>12 months (mean)</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>CRT</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>DEX 0.35</td> <td>-</td> <td>-</td> <td></td> <td></td> <td></td> </tr> <tr> <td>DEX 0.7</td> <td>647.6</td> <td>-118.2</td> <td>NS vs sham</td> <td></td> <td></td> </tr> <tr> <td>Sham</td> <td>619.8</td> <td>-125.3</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>		Baseline	6months (mean)	p	12 months (mean)	p	CRT						DEX 0.35	-	-				DEX 0.7	647.6	-118.2	NS vs sham			Sham	619.8	-125.3														
	Baseline	6months (mean)	p	12 months (mean)	p																																					
CRT																																										
DEX 0.35	-	-																																								
DEX 0.7	647.6	-118.2	NS vs sham																																							
Sham	619.8	-125.3																																								
TRIAMCINOLONE																																										
<p>SCORE 2009 ff.¹⁹⁻³²</p> <p>1 mg intravitreal triamcinolone (2.2 injections over 12 months) (n=92)</p> <p>versus 4 mg intravitreal triamcinolone (2</p>	<p>BCVA (ETDRS letters):</p> <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>12 months</th> <th>p</th> <th>24 months</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>BCVA (letters, 95% CI)</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Tria 1 mg</td> <td>50.6 SD 14.9</td> <td>-1.2 (-6.4 to +4.1)</td> <td><0.05 vs obs</td> <td>-4.4 (-11.5 to +2.8)</td> <td>NR</td> </tr> <tr> <td>Tria 4 mg</td> <td>51.0 SD 14.4</td> <td>-1.2 (-6.3 to +4.0)</td> <td><0.05 vs obs</td> <td>-2.4 (-9.3 to +4.4)</td> <td></td> </tr> </tbody> </table>		Baseline	12 months	p	24 months	p	BCVA (letters, 95% CI)						Tria 1 mg	50.6 SD 14.9	-1.2 (-6.4 to +4.1)	<0.05 vs obs	-4.4 (-11.5 to +2.8)	NR	Tria 4 mg	51.0 SD 14.4	-1.2 (-6.3 to +4.0)	<0.05 vs obs	-2.4 (-9.3 to +4.4)		<p>Ocular Adverse Events</p> <table border="1"> <thead> <tr> <th>AE</th> <th>Tria 1 mg</th> <th>Tria 4 mg</th> <th>Obs</th> </tr> </thead> <tbody> <tr> <td>12 months</td> <td></td> <td></td> <td></td> </tr> <tr> <td><i>Elevated IOP or glaucoma</i></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Initiation of IOP-lowering medication</td> <td>20%</td> <td>35%</td> <td>8%</td> </tr> </tbody> </table>	AE	Tria 1 mg	Tria 4 mg	Obs	12 months				<i>Elevated IOP or glaucoma</i>				Initiation of IOP-lowering medication	20%	35%	8%
	Baseline	12 months	p	24 months	p																																					
BCVA (letters, 95% CI)																																										
Tria 1 mg	50.6 SD 14.9	-1.2 (-6.4 to +4.1)	<0.05 vs obs	-4.4 (-11.5 to +2.8)	NR																																					
Tria 4 mg	51.0 SD 14.4	-1.2 (-6.3 to +4.0)	<0.05 vs obs	-2.4 (-9.3 to +4.4)																																						
AE	Tria 1 mg	Tria 4 mg	Obs																																							
12 months																																										
<i>Elevated IOP or glaucoma</i>																																										
Initiation of IOP-lowering medication	20%	35%	8%																																							

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events			
	CRT						Retinal detachment (n)	0	0	0
	Triia 1 mg	643 SD 226	-196 (-390 to -62)	NR	-286 (-458 to -119)	NR	Iris neovascularisation or neovascular glaucoma	9	4	2
	Triia 4 mg	641 SD 248	-261 (-407 to -79)		-236 (-421 to -63)		Retinal neovascularisation (n)	2	2	4
	Obs	695 SD 208	-277 (-418 to -40)		-304 (-465 to -108)		Vitreous hemorrhage (n)	4	0	4
	CRT <250 µm			CRT <250 µm			<i>Other ocular surgical procedures</i>			
	Triia 1 mg		32%	NR	50%	NR	YAG capsulotomy	0	0	1
	Triia 4 mg		45%		39%		Sector or panretinal scatter photocoagulation	9	3	5
	Obs		28%		38%		Pars plana vitrectomy	2	0	1
	Results for subgroups (based on baseline BCVA (73 to 59, 58 to 49, 48 to 19), baseline CRT (<500 µm, ≥500 µm), duration of macular oedema (≤3 months, >3 months, pseudophakic at baseline) were consistent with the overall results (significance levels for comparisons not reported)						Selected Events at 12-24 months			
							<i>Glaucoma procedures</i>			
							Laser peripheral iridotomy	0	0	0

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events																																																														
		<table border="1"> <tr> <td>Trabeculectomy</td> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td>Tube shunt</td> <td>0</td> <td>2</td> <td>0</td> </tr> <tr> <td colspan="4"><i>Cataract</i></td> </tr> <tr> <td>Cataract surgery</td> <td>3</td> <td>21</td> <td>0</td> </tr> </table> <p>Reports of systemic adverse events were similar between groups</p>	Trabeculectomy	0	0	0	Tube shunt	0	2	0	<i>Cataract</i>				Cataract surgery	3	21	0																																														
Trabeculectomy	0	0	0																																																													
Tube shunt	0	2	0																																																													
<i>Cataract</i>																																																																
Cataract surgery	3	21	0																																																													
ROVO 2013³³ 4 mg intravitreal triamcinolone acetonide (single injection) versus radial optical neurotomy versus sham injection	BCVA (logMAR): <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>12 months</th> <th>p</th> </tr> </thead> <tbody> <tr> <td colspan="4">BCVA (logMAR, interquartile range)</td> </tr> <tr> <td><i>Tria 4 mg</i></td> <td>1.02 (0.75, 2.0)</td> <td>0.86 (0.51, 1.78) (-0.16)</td> <td>NR</td> </tr> <tr> <td><i>RON</i></td> <td>1.46 (0.84, 2.0)</td> <td>0.75 (46, 1.22) (-0.71)</td> <td></td> </tr> <tr> <td><i>Sham</i></td> <td>1.02 (0.9, 1.36)</td> <td>1.02 (0.85, 3.0) (0)</td> <td></td> </tr> </tbody> </table> % with VA improvement <table border="1"> <tbody> <tr> <td><i>Tria 4 mg</i></td> <td>20%</td> <td>0.034 vs RON, NS vs placebo</td> </tr> <tr> <td><i>RON</i></td> <td>47%</td> <td></td> </tr> </tbody> </table>		Baseline	12 months	p	BCVA (logMAR, interquartile range)				<i>Tria 4 mg</i>	1.02 (0.75, 2.0)	0.86 (0.51, 1.78) (-0.16)	NR	<i>RON</i>	1.46 (0.84, 2.0)	0.75 (46, 1.22) (-0.71)		<i>Sham</i>	1.02 (0.9, 1.36)	1.02 (0.85, 3.0) (0)		<i>Tria 4 mg</i>	20%	0.034 vs RON, NS vs placebo	<i>RON</i>	47%		Ocular Adverse Events, 12 months <table border="1"> <thead> <tr> <th>AE</th> <th>Tria 4 mg</th> <th>RON</th> <th>Pla</th> </tr> </thead> <tbody> <tr> <td>Retinal detachment</td> <td></td> <td>7.9%</td> <td></td> </tr> <tr> <td>Subretinal haemorrhages</td> <td></td> <td>5.3%</td> <td></td> </tr> <tr> <td>Vitreous haemorrhage</td> <td></td> <td>2.6%</td> <td>10%</td> </tr> <tr> <td>Subretinal membrane formation</td> <td></td> <td>2.6%</td> <td></td> </tr> <tr> <td>Retinal tear</td> <td></td> <td>2.6%</td> <td></td> </tr> <tr> <td>IOP increase</td> <td>32%</td> <td></td> <td></td> </tr> <tr> <td>Cataract progression</td> <td>24%</td> <td>13%</td> <td>15%</td> </tr> <tr> <td>Neovascular glaucoma</td> <td>12%</td> <td>5%</td> <td>15%</td> </tr> </tbody> </table>	AE	Tria 4 mg	RON	Pla	Retinal detachment		7.9%		Subretinal haemorrhages		5.3%		Vitreous haemorrhage		2.6%	10%	Subretinal membrane formation		2.6%		Retinal tear		2.6%		IOP increase	32%			Cataract progression	24%	13%	15%	Neovascular glaucoma	12%	5%	15%
	Baseline	12 months	p																																																													
BCVA (logMAR, interquartile range)																																																																
<i>Tria 4 mg</i>	1.02 (0.75, 2.0)	0.86 (0.51, 1.78) (-0.16)	NR																																																													
<i>RON</i>	1.46 (0.84, 2.0)	0.75 (46, 1.22) (-0.71)																																																														
<i>Sham</i>	1.02 (0.9, 1.36)	1.02 (0.85, 3.0) (0)																																																														
<i>Tria 4 mg</i>	20%	0.034 vs RON, NS vs placebo																																																														
<i>RON</i>	47%																																																															
AE	Tria 4 mg	RON	Pla																																																													
Retinal detachment		7.9%																																																														
Subretinal haemorrhages		5.3%																																																														
Vitreous haemorrhage		2.6%	10%																																																													
Subretinal membrane formation		2.6%																																																														
Retinal tear		2.6%																																																														
IOP increase	32%																																																															
Cataract progression	24%	13%	15%																																																													
Neovascular glaucoma	12%	5%	15%																																																													

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				Adverse events						
	<i>Sham</i>	10%		0.009 vs RON	Rubeosis iridis 15% No cases of phthisis, enucleation, endophthalmitis, injury of central vessels, injury of optic nerve						
	% with VA deterioration										
	<i>Tria 4 mg</i>	NR									
	<i>RON</i>	8%									
	<i>Sham</i>	35%									
	CRT (µm):										
			Baseline	12 months				p			
	CRT										
	<i>Tria 4 mg</i>	657	-235					NS			
	<i>RON</i>	569	-263					NS			
<i>Sham</i>	615	-206									
AFLIBERCEPT											
COPERNICUS 2012 ^{34;35} 2 mg intravitreal aflibercept (every 4 weeks over 24	BCVA (ETDRS letters):				Adverse Events						
			Baseline	24 weeks	p	52 weeks (all VTE PRN)	p	AE (24 weeks) VTE Sham			
	BCVA (letters)							Discontinued treatment before week 24 because of AE 0 4.1%			
							At least one AE 83.3% 85.1%				

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events			
weeks)(n=114) versus sham injection (n=73)	VTE	50.7 SD 13.9	+17.3	<0.001	+16.2	<0.001	Ocular AEs	68.4%	68.9%	
	Sham	48.9 SD 14.4	-4.0		+3.8		Patients with at least one serious adverse event	3.5%	13.5%	
extension up to 52 weeks with afibercept PRN in both groups	≥15 letters gained						Vitreous haemorrhage	0	5.4%	
	VTE		56.1%	<0.001	55.3%	<0.001	Neovascular glaucoma	0	2.7%	
	Sham		12.3%		30.1%		Iris neovascularisation	0	2.7%	
	≥10 letters lost						Retinal haemorrhage	0	2.7%	
	VTE		1.8%	NR			Visual acuity reduced	0.9%	1.4%	
	Sham		30.1%				Retinal artery occlusion	0.9%	0	
	Subgroups						Retinal tear	0	1.4%	
	Baseline VA		≥15 letters gained				Retinal vein occlusion	0	1.4%	
	VTE ≤20/200	VTE		67.9%	NR	60.7%	NR	Endophthalmitis	0.9%	0
		Sham		16.7%		22.2%		Corneal abrasion	0.9%	0
VTE >20/200	VTE		52.3%		53.5%		AE (24 to 52 weeks)	VTE	Sham	
	Sham		10.9%		32.7%		Patients with at least one serious adverse event	2.7%	3.3%	
Time since diagnosis						Vitreous haemorrhage	0.9%	1.7%		
VTE <2 mo	VTE		68.8%	NR	64.1%	NR	Glaucoma	0	1.7%	

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events		
	<i>Sham</i>		15.4%			34.6%	Iris neovascularisation	0	0
	VTE ≥2 mo	<i>VTE</i>	38.8%			42.9%	Retinal haemorrhage	0	0
	<i>Sham</i>		4.8%			19.0%	Visual acuity reduced	0	0
	Perfusion status						Retinal artery occlusion	0	0
	VTE perfused	<i>VTE</i>	58.4%	NS		58.4%	Retinal tear	0	1.7%
		<i>Sham</i>	16%			30.0%	Retinal vein occlusion	0.9%	0
	VTE non-perfused	<i>VTE</i>	51.4%			48.6%	Cataract	0.9%	0
		<i>Sham</i>	4.3%			30.4%	Cystoid macular oedema	0.9%	0
	CRT (µm):						Endophthalmitis	0	0
		Baseline	24 weeks	p		52 weeks (all VTE PRN)	p		
	CRT								
	<i>VTE</i>	661.7 SD 237.4	-457.2	<0.001		-413.0	NS		
	<i>Sham</i>	672.4 SD 245.3	-144.8			-381.8			
	QoL								
		Baseline	24 weeks	p		52 weeks (all VTE PRN)	p		

Reports of systemic adverse events were similar between groups; 2 deaths in the sham group by 24 weeks; 2.7% arterial thromboembolic events in the sham group and 0.9% in the intervention group

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events
	PRN)						
	NEI-VFQ-25 total						
	VTE	77.76 SD 15.96	+7.2 SD 12.1	0.001	+7.5	NS	
	Sham	77.78 SD 16.25	+0.8 SD 9.8		+5.1		
	NEI-VFQ-25 near activities						
	VTE	69.96 SD 21.94	+8.3 SD 22.0	<0.05	+11.4	NS	
	Sham	70.72 SD 20.22	+1.84 SD 19.75		+8.3		
	NEI-VFQ-25 distance activities						
	VTE	75.99 SD 21.26	+6.1 SD 20.0	<0.05	+8.5	NS	
	Sham	78.08 SD 21.25	-0.64 SD 15.2		+3.8		
	NEI-VFQ-25 vision dependency						
	VTE	83.26 SD 25.51	+7.1 SD 20.5	<0.05	+6.0	NS	
	Sham	82.76 SD 27.41	+1.1 SD 20.5		+3.4		

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events																																																																																																																								
	Progression to neovascularisation: 0 with aflibercept, 6.8% with sham treatment over 52 weeks, p=0.006 Perfused status at week 24: 78.9% with aflibercept, 46.6% with sham treatment																																																																																																																									
GALILEO 2012^{36,37} 2 mg intravitreal aflibercept (every 4 weeks over 24 weeks) (n=103) versus sham injection (n=71) extension up to 52 weeks	BCVA (ETDRS letters): <table border="1" data-bbox="394 500 1434 1339"> <thead> <tr> <th></th> <th>Baseline</th> <th>24 weeks</th> <th>p</th> <th>52 weeks</th> <th>p</th> </tr> </thead> <tbody> <tr> <td colspan="6">BCVA (letters)</td> </tr> <tr> <td>VTE</td> <td>53.6 SD15.8</td> <td>+18.0</td> <td><0.0001</td> <td>+16.9</td> <td><0.0001</td> </tr> <tr> <td>Sham</td> <td>50.9 SD15.4</td> <td>+3.3</td> <td></td> <td>+3.8</td> <td></td> </tr> <tr> <td colspan="6">≥15 letters gained</td> </tr> <tr> <td>VTE</td> <td></td> <td>60.2%</td> <td><0.0001</td> <td>60.2%</td> <td>0.0004</td> </tr> <tr> <td>Sham</td> <td></td> <td>22.1%</td> <td></td> <td>32.4%</td> <td></td> </tr> <tr> <td colspan="6">≥10 letters lost</td> </tr> <tr> <td>VTE</td> <td></td> <td>7.8%</td> <td>0.0033</td> <td></td> <td></td> </tr> <tr> <td>Sham</td> <td></td> <td>25.0%</td> <td></td> <td></td> <td></td> </tr> <tr> <td colspan="6">Subgroups</td> </tr> <tr> <td colspan="2">Time since diagnosis</td> <td colspan="4">≥15 letters gained</td> </tr> <tr> <td>VTE <2 mo</td> <td></td> <td>70.9%</td> <td>NR</td> <td></td> <td></td> </tr> </tbody> </table>		Baseline	24 weeks	p	52 weeks	p	BCVA (letters)						VTE	53.6 SD15.8	+18.0	<0.0001	+16.9	<0.0001	Sham	50.9 SD15.4	+3.3		+3.8		≥15 letters gained						VTE		60.2%	<0.0001	60.2%	0.0004	Sham		22.1%		32.4%		≥10 letters lost						VTE		7.8%	0.0033			Sham		25.0%				Subgroups						Time since diagnosis		≥15 letters gained				VTE <2 mo		70.9%	NR			Ocular Adverse Events <table border="1" data-bbox="1501 500 2055 1339"> <thead> <tr> <th>AE</th> <th>VTE</th> <th>Sham</th> </tr> </thead> <tbody> <tr> <td>Discontinued treatment before week 24 because of AE</td> <td>1.9%</td> <td>11.3%</td> </tr> <tr> <td>Eye pain</td> <td>11.5%</td> <td>4.4%</td> </tr> <tr> <td>Conjunctival haemorrhage</td> <td>8.7%</td> <td>4.4%</td> </tr> <tr> <td>Retinal exudates</td> <td>6.7%</td> <td>7.4%</td> </tr> <tr> <td>Foreign body sensation</td> <td>5.8%</td> <td>7.4%</td> </tr> <tr> <td>Retinal vascular disorder</td> <td>5.8%</td> <td>8.8%</td> </tr> <tr> <td>Ocular hyperaemia</td> <td>4.8%</td> <td>5.9%</td> </tr> <tr> <td>Vitreous floaters</td> <td>4.8%</td> <td>0</td> </tr> <tr> <td>Macular oedema</td> <td>3.8%</td> <td>16.2%</td> </tr> <tr> <td>Macular ischaemia</td> <td>3.8%</td> <td>4.4%</td> </tr> <tr> <td>Optic disc vascular disorder</td> <td>3.8%</td> <td>4.4%</td> </tr> <tr> <td>Eye irritation</td> <td>2.9%</td> <td>10.3%</td> </tr> <tr> <td>Lacrimation increased</td> <td>2.9%</td> <td>5.9%</td> </tr> </tbody> </table>	AE	VTE	Sham	Discontinued treatment before week 24 because of AE	1.9%	11.3%	Eye pain	11.5%	4.4%	Conjunctival haemorrhage	8.7%	4.4%	Retinal exudates	6.7%	7.4%	Foreign body sensation	5.8%	7.4%	Retinal vascular disorder	5.8%	8.8%	Ocular hyperaemia	4.8%	5.9%	Vitreous floaters	4.8%	0	Macular oedema	3.8%	16.2%	Macular ischaemia	3.8%	4.4%	Optic disc vascular disorder	3.8%	4.4%	Eye irritation	2.9%	10.3%	Lacrimation increased	2.9%	5.9%
	Baseline	24 weeks	p	52 weeks	p																																																																																																																					
BCVA (letters)																																																																																																																										
VTE	53.6 SD15.8	+18.0	<0.0001	+16.9	<0.0001																																																																																																																					
Sham	50.9 SD15.4	+3.3		+3.8																																																																																																																						
≥15 letters gained																																																																																																																										
VTE		60.2%	<0.0001	60.2%	0.0004																																																																																																																					
Sham		22.1%		32.4%																																																																																																																						
≥10 letters lost																																																																																																																										
VTE		7.8%	0.0033																																																																																																																							
Sham		25.0%																																																																																																																								
Subgroups																																																																																																																										
Time since diagnosis		≥15 letters gained																																																																																																																								
VTE <2 mo		70.9%	NR																																																																																																																							
AE	VTE	Sham																																																																																																																								
Discontinued treatment before week 24 because of AE	1.9%	11.3%																																																																																																																								
Eye pain	11.5%	4.4%																																																																																																																								
Conjunctival haemorrhage	8.7%	4.4%																																																																																																																								
Retinal exudates	6.7%	7.4%																																																																																																																								
Foreign body sensation	5.8%	7.4%																																																																																																																								
Retinal vascular disorder	5.8%	8.8%																																																																																																																								
Ocular hyperaemia	4.8%	5.9%																																																																																																																								
Vitreous floaters	4.8%	0																																																																																																																								
Macular oedema	3.8%	16.2%																																																																																																																								
Macular ischaemia	3.8%	4.4%																																																																																																																								
Optic disc vascular disorder	3.8%	4.4%																																																																																																																								
Eye irritation	2.9%	10.3%																																																																																																																								
Lacrimation increased	2.9%	5.9%																																																																																																																								

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events		
	VTE ≥2 mo		50.0%				Papilloedema	1.9%	4.4%
	CRT (µm):						Retinal ischaemia	1.0%	4.4%
		Baseline	24 weeks	p	52 weeks	p	Visual acuity reduced	0	10.3%
	CRT						IOP increased	9.6%	5.9%
	VTE	683.2 SD234.5	-448.6	<0.0001	-423.5	<0.0001	Injection site pain	4.8%	2.9%
	Sham	638.7 SD224.7	-169.3		-219.3		Serious adverse events		
	QoL						At least 1 SAE	1.9%	5.9%
		Baseline	24 weeks	p	52 weeks	p	Glaucoma	0	2.9%
	NEI-VFQ						Macular oedema	1.0%	1.5%
	VTE		+7.5	0.0013			Retinal tear	1.0%	0
	Sham		+3.5				Vitreous detachment	1.0%	0
	Percentage of any patients progressing to any neovascularisation by week 24, difference between groups -1.5 (95% CI: -7.4 to 4.4)						Reports of systemic adverse events were similar between groups; no arterial thromboembolic events or deaths during 24 weeks		
	No significant differences on the EQ-5D score between groups						No endophthalmitis or cases of rhegmatogenous detachment, one incidence of uveitis in VTE group considered mild and resolved without change in therapy		

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events																																																						
PEGAPTANIB																																																								
Wroblewski 2009³⁸⁻⁴⁴ 0.3 mg intravitreal pegaptanib sodium (every 6 weeks over 24 weeks) (n=33) versus 1 mg intravitreal pegaptanib sodium (every 6 weeks over 24 weeks) (n=33) versus sham injection (n=32) FU up to 52 weeks	BCVA (ETDRS letters): <table border="1" data-bbox="394 402 1430 467"> <thead> <tr> <th></th> <th>Baseline</th> <th>30 weeks</th> <th>p</th> <th>52 weeks</th> <th>p</th> </tr> </thead> <tbody> <tr> <td colspan="6">BCVA (letters)</td> </tr> <tr> <td><i>PS 0.3 mg</i></td> <td>47.6</td> <td>+7.1</td> <td>NS, 0.09 vs sham</td> <td>+7.5</td> <td>NS vs sham</td> </tr> <tr> <td><i>PS 1 mg</i></td> <td>48.4</td> <td>+9.9</td> <td>0.02 vs sham</td> <td>+6.3</td> <td>NS vs sham</td> </tr> <tr> <td><i>Sham</i></td> <td>48.5</td> <td>-3.2</td> <td></td> <td>-2.4</td> <td></td> </tr> </tbody> </table> <table border="1" data-bbox="394 737 1430 834"> <thead> <tr> <th colspan="3">≥15 letters gained</th> </tr> </thead> <tbody> <tr> <td><i>PS 0.3 mg</i></td> <td>36%</td> <td>NS, p=0.48</td> </tr> <tr> <td><i>PS 1 mg</i></td> <td>39%</td> <td></td> </tr> <tr> <td><i>Sham</i></td> <td>28%</td> <td></td> </tr> </tbody> </table> <table border="1" data-bbox="394 1013 1430 1240"> <thead> <tr> <th colspan="3">≥15 letters lost</th> </tr> </thead> <tbody> <tr> <td><i>PS 0.3 mg</i></td> <td>9%</td> <td>0.03 vs sham</td> </tr> <tr> <td><i>PS 1 mg</i></td> <td>6%</td> <td>0.01 vs sham</td> </tr> <tr> <td><i>Sham</i></td> <td>31%</td> <td></td> </tr> </tbody> </table> CRT (μm):		Baseline	30 weeks	p	52 weeks	p	BCVA (letters)						<i>PS 0.3 mg</i>	47.6	+7.1	NS, 0.09 vs sham	+7.5	NS vs sham	<i>PS 1 mg</i>	48.4	+9.9	0.02 vs sham	+6.3	NS vs sham	<i>Sham</i>	48.5	-3.2		-2.4		≥15 letters gained			<i>PS 0.3 mg</i>	36%	NS, p=0.48	<i>PS 1 mg</i>	39%		<i>Sham</i>	28%		≥15 letters lost			<i>PS 0.3 mg</i>	9%	0.03 vs sham	<i>PS 1 mg</i>	6%	0.01 vs sham	<i>Sham</i>	31%		No serious ocular adverse events up to week 30 No endophthalmitis, traumatic cataract or retinal detachment (30 weeks) No evidence of sustained effect on intraocular pressure (30 weeks) No evidence of increased risk of systemic adverse events (30 weeks)
	Baseline	30 weeks	p	52 weeks	p																																																			
BCVA (letters)																																																								
<i>PS 0.3 mg</i>	47.6	+7.1	NS, 0.09 vs sham	+7.5	NS vs sham																																																			
<i>PS 1 mg</i>	48.4	+9.9	0.02 vs sham	+6.3	NS vs sham																																																			
<i>Sham</i>	48.5	-3.2		-2.4																																																				
≥15 letters gained																																																								
<i>PS 0.3 mg</i>	36%	NS, p=0.48																																																						
<i>PS 1 mg</i>	39%																																																							
<i>Sham</i>	28%																																																							
≥15 letters lost																																																								
<i>PS 0.3 mg</i>	9%	0.03 vs sham																																																						
<i>PS 1 mg</i>	6%	0.01 vs sham																																																						
<i>Sham</i>	31%																																																							

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events			
	Baseline	30 weeks	p	52 weeks	p				
	CRT								
	PS 0.3 mg	688	-243	NS, p=0.13	-295	<0.05 vs sham			
	PS 1 mg	632	-179	NS, p=0.06	-216				
	Sham	674	-148			-183			
	3 patients in the sham arm and 1 patient in each of the pegaptanib sodium arms developed ocular neovascularisation (p=0.29 (NS))								
RANIBIZUMAB									
CRUISE 2010 ff. ^{10;45;46}	BCVA (ETDRS letters):					6 months			
	Baseline	6 months	12 months (ran PRN)		24 months (ran PRN, HORIZON)	AE	Ran 0.3 mg	Ran 0.5 mg	Sham
0.3 mg intravitreal ranibizumab (monthly for 6 months)	BCVA (letters, 95% CI)					Any intraocular inflammation event			
	Ran 0.3 mg	47.4 SD14.8	+12.7 (9.9, 15.4), p<0.0001 vs sham	+13.9 SD15.2, p=0.0007 vs sham	+8.2	Iridocyclitis	2.3 %	1.6%	3.9%
versus 0.5 mg intravitreal ranibizumab (monthly for 6 months)	Ran 0.5 mg	48.1 SD14.6	+14.9 (12.6, 17.2), p<0.0001 vs sham	+13.9 SD14.2, p=0.0006 vs sham	+12.0	Iritis	1.5%	1.6%	2.3%
	Sham	49.2 SD14.7	+0.8 (-2.0, 3.6)	+7.3 SD15.9	+7.6	Vitritis	0.8%	0.8%	1.6%
						Endophthalmitis	0	0	0

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				Adverse events			
versus sham	≥15 letters gained				Lens damage	0	0	0
extension 6 to 12 months 0.3 or 0.5 mg ranibizumab PRN	Ran 0.3 mg	46.2%, p<0.0001 vs sham	47.0%	38.6%	Cataract	1.5%	1.6%	0
extension ≥12 to 24 months 0.5 mg ranibizumab PRN	Ran 0.5 mg	47.7%, p<0.0001 vs sham	50.8%	45.1%	Iris neovascularisation	1.5%	0.8%	7.0%
	Sham	16.9%	33.1%	38.3%	Neovascular glaucoma	0	0	1.6%
	≥15 letters lost				Rhegmatogenous retinal detachment	0	0	0
	Ran 0.3 mg	3.8%	3.8%	12.9%	Retinal tear	0	0	0
	Ran 0.5 mg	1.5%	2.3%	5.9%	Vitreous haemorrhage	3.8%	5.4%	7.0%
	Sham	15.4%	10.0%	13.3%	Systemic adverse events balanced across groups; 1 myocardial infarction in each group, 1 transient ischaemic attack and angina pectoris in the same person in ran 0.5 mg group			
	Subgroups				12 months, sham for months 6 to 12			
	Time of diagnosis (6 month outcomes): <3 months: +13.2 letters (both ran groups), ≥3 months: +10.5 letters (0.3 mg ran), +15.3 letters (0.5 mg ran), p=?				Ocular AE	Ran	Ran	Sham
	Mean change in BCVA was greater for patients with worse baseline BCVA and CRT >450 μm					0.3	0.5	
	CRT (μm) and anatomic					mg	mg	
	Baseline	6 months	12 months (ran PRN)	24 months (ran PRN, HORIZON)	Any intraocular inflammation	2.3 %	1.6%	1.8%

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				Adverse events				
	CRT (μm, 95% CI)				event				
	Ran 0.3 mg	679.9 SD 242.4	-433.7 (-484.9, -382.6), p<0.0001 vs sham	-462.1, p= NS vs sham	-370.9				
	Ran 0.5 mg	688.7 SD 253.1	-452.3 (-497.0, -407.6), p<0.0001 vs sham	-452.8, p=NS vs sham	-412.2				
	Sham	687.0 SD 237.6	-167.7 (-221.5 -114.0)	-427.2	-418.7				
	CRT $\leq 250 \mu\text{m}$								
	Ran 0.3 mg		75.0%, p<0.0001 vs sham	75.8%	58.0%				
	Ran 0.5 mg		76.9%, p<0.0001 vs sham	77.7%	56.9%				
	Sham		23.1%	70.8%	70.2%				
	No retinal haemorrhages								
	Ran 0.3 mg		0.8%	31.5%	41.3%				
	Ran 0.5 mg		1.5%	39.3%	47.8%				
	Sham		1.5%	5.4%	36.7%				
	QoL								
					HORIZON, 12 to 24 months				
					AE	Ran 0.3/0.5	Ran 0.5	Sham/ran 0.5 mg	
						0	0	0	
						0	0	0	
						3.8%	7.0%	1.8%	
						1.5%	3.9%	1.8%	
						0	0.8%	0	
						0	0	0	
						0	1.6%	1.8%	
						5.3%	5.4%	1.8%	
						0.8%	2.3%	0	

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events			
	Baseline	6 months	p	12 months (ran PRN)	p		mg	mg	
	NEI-VFQ (95% CI)					Any ocular AE	62.6%	66.7%	62.5%
	Ran 0.3 mg	+7.1 (5.2, 9.0)	<0.05 vs sham	+7.1	NS vs sham	Ocular AEs leading to discontinuation	1.9%	2.0%	0
	Ran 0.5 mg	+6.2 (4.3, 8.0)	<0.05 vs sham	+6.6	NS vs sham	Cataract	5.6%	5.1%	3.1%
	Sham	+2.8 (0.8, 4.7)		+5.0		Ocular serious adverse events	9.3%	3.0%	5.2%
						Cystoid macular oedema	0.9%	0	0
						Endophthalmitis	1.9%	0	0
						IOP increased	0.9%	0	0
						Macular oedema	1.9%	2.0%	1.0%
						Ischaemic optic neuropathy	0.9%	0	0
						VA reduced	1.9%	1.0%	3.1%
						VA reduced transiently	0.9%	0	0
						Vitreous haemorrhage	0	0	1.0%
						Arterial thromboembolic	1.9%	3.0%	2.1%

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events																																																						
		events (potentially related to drug)																																																						
BEVACIZUMAB																																																								
<p>Epstein 2012⁴⁷⁻⁴⁹</p> <p>1.25 mg intravitreal bevacizumab (4 injections over 6 months) (n=30) versus sham injection (n=30)</p> <p>6 month open label extension (1.25 mg intravitreal bevacizumab (4 injections over 6 months) for all patients)</p>	<p>BCVA (ETDRS letters):</p> <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>24 weeks</th> <th>p</th> <th>48 weeks (bev/bev vs sham/bev)</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>BCVA (letters)</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Bev</td> <td>44.4 SD15.3; 30% <34, 70% >34</td> <td>+14.1</td> <td><0.01</td> <td>+16.1</td> <td><0.05</td> </tr> <tr> <td>Sham</td> <td>43.9 SD16.0; 33.3% <34, 66.7% >34</td> <td>-2.0</td> <td></td> <td>+4.6</td> <td></td> </tr> <tr> <td>≥15 letters gained</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Bev</td> <td></td> <td>60%</td> <td>0.003</td> <td>60%</td> <td><0.05</td> </tr> <tr> <td>Sham</td> <td></td> <td>20%</td> <td></td> <td>33.3%</td> <td></td> </tr> <tr> <td>>15 letters lost</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Bev</td> <td></td> <td>6.7%</td> <td>NS, p=0.146</td> <td>6.7%</td> <td>NS</td> </tr> </tbody> </table>		Baseline	24 weeks	p	48 weeks (bev/bev vs sham/bev)	p	BCVA (letters)						Bev	44.4 SD15.3; 30% <34, 70% >34	+14.1	<0.01	+16.1	<0.05	Sham	43.9 SD16.0; 33.3% <34, 66.7% >34	-2.0		+4.6		≥15 letters gained						Bev		60%	0.003	60%	<0.05	Sham		20%		33.3%		>15 letters lost						Bev		6.7%	NS, p=0.146	6.7%	NS	<p>Adverse events:</p> <p>Neovascularisation: 16.7% (sham) versus 0 (bev) had developed iris rubeosis at week 24; iris rubeosis regressed in all patients at week 48, no new cases in either group</p> <p>No events of endophthalmitis, retinal tear, retinal detachment; no serious non-ocular adverse events</p>
	Baseline	24 weeks	p	48 weeks (bev/bev vs sham/bev)	p																																																			
BCVA (letters)																																																								
Bev	44.4 SD15.3; 30% <34, 70% >34	+14.1	<0.01	+16.1	<0.05																																																			
Sham	43.9 SD16.0; 33.3% <34, 66.7% >34	-2.0		+4.6																																																				
≥15 letters gained																																																								
Bev		60%	0.003	60%	<0.05																																																			
Sham		20%		33.3%																																																				
>15 letters lost																																																								
Bev		6.7%	NS, p=0.146	6.7%	NS																																																			

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				Adverse events
	<i>Sham</i>	23.3%	6.7%		
	Subgroups				
	Disease duration	BCVA (letters)			
	<i>Bev <90 days</i>	+18.7	0.039		
	<i>Bev >90 days</i>	+9.8			
	Age	BCVA (letters)			
	<i><70 years</i>	+14.2	NS, >0.05		
	<i>>70 years</i>	+7.4			
	<i><70 years sham/bev</i>	-1.4	<0.003		
	<i>>70 years sham/bev</i>	+20.1			
	CRT (µm):				
	Baseline	24 weeks	p	48 weeks (bev/bev vs sham/bev)	p

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events
	CRT					
	<i>Bev/bev</i>	712 SD330	-426	<0.001	-435	NS, >0.05
	<i>Sham/bev</i>	729 SD195	-102		-404	
	No residual oedema (CRT <300 μm)					
	<i>Bev/bev</i>		86.7%	<0.001	83.3%	NS
	<i>Sham/bev</i>		20%		60%	

7 **Abbreviations:** AE – adverse event, BCVA – best corrected visual acuity, CI – confidence interval, CRT – central retinal thickness, CRVO – central retinal vein
8 occlusion, ETDRS – Early Treatment Diabetic Retinopathy Study, FU – follow-up, IQR – interquartile range, IOP – intraocular pressure, mo – months, NR –
9 not reported, NS – non-significant, OCT – optical coherence tomography, PRN – pro re nata (as needed), QoL – quality of life, SD – standard deviation

11 Table 3: Study quality

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
DEXAMETHASONE							
GENEVA 2010 ff.	Low	Low	Partial: patients and assessors of efficacy variables	Low: ITT analysis, 94% FU at 6 months	Low	<i>Power: 81% power to detect difference in primary outcome with n=495 for each trial</i> <i>Similarity at baseline: yes</i>	Allergan Inc.
TRIAMCINOLONE							
SCORE 2009 ff	Low	Unclear	Partial (physicians and patients masked to dose but not triamcinolone versus observation)	Low: ITT analysis, 83 to 90% FU at 12 months	Low	<i>Power: 80% power to detect difference in primary outcome with n=486 (but only 271 randomised)</i> <i>Similarity at baseline: yes</i>	National Eye Institute grants, Allergan

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
ROVO 2013	Low	Low	Unclear	Low: ITT analysis (?), 92% FU at 12 months	Low	<i>Power:</i> 80% power to detect difference in primary outcome with n=53 per group (but only 20 to 38 per group) <i>Similarity at baseline:</i> unclear <i>Other:</i> limited baseline data	Jubiläumsfonds der Österreichischen Nationalbank, Ludwig Boltzmann Institute for Retinology and Biomicroscopic Laser Surgery (non-commercial)
AFLIBERCEPT							
COPERNICUS 2012	Low	Unclear	Low: double-blind	Low: ITT analysis, 89.9% assessed at primary end point	Low	<i>Power:</i> 90% power to detect difference in primary outcome with n=165 <i>Similarity at baseline:</i> yes	Bayer HealthCare, Regeneron Pharmaceuticals

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
GALILEO 2012	Unclear	Unclear	Low: double-blind	Low: ITT analysis, 86% assessed at primary end point	Low	Power: 90% power to detect difference in primary outcome with n=150 Similarity at baseline: yes	Bayer HealthCare, Regeneron Pharmaceuticals
PEGAPTANIB							
Wroblewski 2009	Low	Low	Low: patients and ophthalmologist responsible for patients care and assessments	Low: ITT analysis, 7% withdrawals	Low	Power: 80% power to detect difference in primary outcome with n=30 per group Similarity at baseline: yes	Eyetech Inc, Pfizer Inc.
RANIBIZUMAB							
CRUISE 2010 ff	Low	Unclear	Low: patients and evaluating examiners, injecting physicians masked to dose	Low: ITT analysis, 88.5 to 97.7% completed 6 months	Low	Power: not reported Similarity at baseline: yes	Genentech Inc.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
BEVACIZUMAB							
Epstein 2012	Unclear	Low	Low: patients, outcome assessors	Low: ITT analysis; missing data for 2 patients (primary endpoint)	Low	<i>Power:</i> 80% power to detect difference in primary outcome with n=24 per group <i>Similarity at baseline:</i> yes	Unclear; authors are consultants for Allergan, Novartis, Alcon, Bayer

12

13

14 Table 4: On-going trials

Study	Participants and baseline values	Intervention / Outcomes
<p data-bbox="174 370 342 394">MINOCYCLINE</p> <p data-bbox="174 431 806 456">http://clinicaltrials.gov/ct2/show/study/NCT01468844</p> <p data-bbox="174 492 226 516">USA</p> <p data-bbox="174 607 726 667">Study aim: to test the safety and effectiveness of minocycline as a treatment for CRVO</p> <p data-bbox="174 699 464 724">Design: RCT, double-blind</p> <p data-bbox="174 756 426 781">Follow-up: 24 months</p>	<p data-bbox="827 431 905 456">N: ~20</p> <p data-bbox="827 548 1419 643">Inclusion criteria:>18 years, macular oedema secondary to CRVO, CRT >350 µm, media clarity and pupillary dilatation sufficient for fundus photographs</p> <p data-bbox="827 675 1451 1003">Exclusion criteria: macular oedema due to causes other than CRVO, history of recurrent RVO or RVO >18 months, any other ocular condition that could affect macular oedema or BCVA, substantial cataract, photocoagulation within 4 months before study, pars plana vitrectomy within 6 months, major ocular surgery within 3 months, study eye treated with intravitreal or periocular steroid injections within 3 months, study eye treated with intravitreal anti-VEGF agents within 28 days; significant systemic disease (details given)</p>	<p data-bbox="1476 431 1902 558">Mino: 100 mg oral minocycline twice daily over 24 months; monthly bevacizumab injection over 3 months, then PRN</p> <p data-bbox="1476 591 1902 685">Placebo: oral placebo twice daily over 24 months; monthly bevacizumab injection over 3 months, then PRN</p> <p data-bbox="1476 776 1850 836">Primary end point: BCVA over 12 months</p> <p data-bbox="1476 868 1877 928">Other outcomes: number of bevacizumab injections, CRT, safety</p> <p data-bbox="1476 961 1871 1021">Outcome assessment: 6, 12, 18, 24 months</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Participants and baseline values	Intervention / Outcomes
BEVACIZUMAB / TRIAMCINOLONE		
<p data-bbox="176 370 684 399">http://clinicaltrials.gov/show/NCT00566761</p> <p data-bbox="176 431 260 461">Mexico</p> <p data-bbox="176 548 777 675">Study aim: to assess if treatment of macular oedema secondary to CRVO is more effective with combined therapy of bevacizumab and triamcinolone compared to bevacizumab alone</p> <p data-bbox="176 708 546 737">Design: RCT, open-label, phase 4</p> <p data-bbox="176 769 428 799">Follow-up: 12 months</p>	<p data-bbox="829 373 907 402">N: ~10</p> <p data-bbox="829 490 1449 552">Inclusion criteria: macular oedema secondary to CRVO; BCVA <20/40; CRT >250 µm (OCT)</p> <p data-bbox="829 639 1449 766">Exclusion criteria: diabetic retinopathy or other retinopathy; media opacity that does not allow follow-up; steroid responder; diagnosed glaucoma or IOP > 21 mmHg</p>	<p data-bbox="1478 373 1885 435">Bev: bevacizumab 2.5 mg for (3 applications, administered monthly)</p> <p data-bbox="1478 467 1915 561">Bev/Tria: bevacizumab 2.5 mg + triamcinolone 4 mg first dose followed by two doses of bevacizumab alone</p> <p data-bbox="1478 649 1852 711">Primary end point: BCVA over 12 months</p> <p data-bbox="1478 743 1793 805">Other outcomes: treatment complications</p> <p data-bbox="1478 837 1860 899">Outcome assessment: 3, 6 and 12 months</p>
RANIBIZUMAB		

Study	Participants and baseline values	Intervention / Outcomes
<p data-bbox="176 315 684 341">http://clinicaltrials.gov/show/NCT01123564</p> <p data-bbox="176 373 275 399">Hungary</p> <p data-bbox="176 490 789 652">Study aim: to assess if ranibizumab (Lucentis) injection applied into the eye is superior to conventional treatment concerning the prevention of visual loss in patients having clinically significant macular oedema secondary to retinal vein occlusion</p> <p data-bbox="176 685 541 711">Design: RCT, open-label, phase 2</p> <p data-bbox="176 743 424 769">Follow-up: 12 months</p>	<p data-bbox="827 315 905 341">N: ~40</p> <p data-bbox="827 431 1449 691">Inclusion criteria: >18 years, macular oedema persisting for >3 months despite conventional medication; CRVO confirmed by slit-lamp biomicroscopy and fluorescein angiography (FLAG); patient in ranibizumab group do not receive macular laser treatment; CRT > 280 µm and/or retinal thickness is >330 µm at any region of the macula; baseline VA <64 ETDRS letters (or 0.4 decimal equivalent)</p> <p data-bbox="827 724 1449 1081">Exclusion criteria: diabetes mellitus; additional vitreoretinal diseases; history of pars plana vitrectomy; previous macular grid laser treatment; intravitreal triamcinolone acetonide treatment; complicated cataract surgery; advanced glaucomatous damage of optic nerve head; cataract (except mild, defined as grade 1 nuclear sclerosis and/or grade 1 posterior subcapsular cataract); age-related macular degeneration; pregnancy and lactation; women in childbearing potential who are not using double safe contraception</p>	<p data-bbox="1478 315 1913 477">Rani: intravitreal ranibizumab, applied monthly in the first 3 months, and after this only if visual acuity (VA) decreases with more than 5 letters at any monthly visits</p> <p data-bbox="1478 509 1898 672">Laser: Argon laser treatment; conventional grid pattern argon laser treatment and panretinal argon laser photocoagulation in an as needed basis</p> <p data-bbox="1478 753 1850 818">Primary end point: BCVA over 12 months</p> <p data-bbox="1478 850 1717 876">Other outcomes: CRT</p> <p data-bbox="1478 909 1892 935">Outcome assessment: monthly visits</p>

References

- 1
2
3 15
4 16
5
6
7 17 (1) Deramo VA, Cox TA, Syed AB, et al. Vision-related quality of life in people with central
8 18 retinal vein occlusion using the 25-item National Eye Institute Visual Function
9 19 Questionnaire. *Arch Ophthalmol* 2003; 121(9):1297-1302.
- 10
11 20 (2) McIntosh RL, Rogers SL, Lim L, et al. Natural history of central retinal vein occlusion: an
12 21 evidence-based systematic review. *Ophthalmology* 2010; 117(6):1113-1123.
- 13
14 22 (3) Mitchell P, Smith W, Chang A. Prevalence and associations of retinal vein occlusion in
15 23 Australia. The Blue Mountains Eye Study. *Arch Ophthalmol* 1996; 114(10):1243-1247.
- 16
17 24 (4) Rogers S, McIntosh RL, Cheung N, et al. The prevalence of retinal vein occlusion: pooled
18 25 data from population studies from the United States, Europe, Asia, and Australia.
19 26 *Ophthalmology* 2010; 117(2):313-319.
- 20
21 27 (5) The Royal College of Ophthalmology. Interim guidelines for management of retinal vein
22 28 occlusion. [http://www.rcophth.ac.uk/core/core_picker/download](http://www.rcophth.ac.uk/core/core_picker/download.asp?id=728&filetitle=Interim+Guidelines+for+Management+of+Retinal+Vein+Occlusion+2010)
23 29 [asp?id=728&filetitle=Interim+Guidelines+for+Management+of+Retinal+Vein+Occlusion+2010](http://www.rcophth.ac.uk/core/core_picker/download.asp?id=728&filetitle=Interim+Guidelines+for+Management+of+Retinal+Vein+Occlusion+2010) [2010 [cited 2013 Sept. 7];
24 30
- 25
26 31 (6) Hayreh SS, Podhajsky PA, Zimmerman MB. Natural history of visual outcome in central
27 32 retinal vein occlusion. *Ophthalmology* 2011; 118(1):119-133.
- 28
29 33 (7) Kiire CA, Chong NV. Managing retinal vein occlusion. *BMJ* 2012; 344:e499.
- 30
31 34 (8) The Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema
32 35 in branch vein occlusion. *Am J Ophthalmol* 1984; 98(3):271-282.
- 33
34 36 (9) The Central Vein Occlusion Study Group. Evaluation of grid pattern photocoagulation for
35 37 macular edema in central vein occlusion. *Ophthalmology* 1995; 102(10):1425-1433.
- 36
37 38 (10) Brown DM, Campochiaro PA, Singh RP, et al. Ranibizumab for macular edema following
38 39 central retinal vein occlusion: six-month primary end point results of a phase III study.
39 40 *Ophthalmology* 2010; 117(6):1124-1133.
- 40
41 41 (11) Haller JA, Bandello F, Belfort R, Jr., et al. Randomized, sham-controlled trial of
42 42 dexamethasone intravitreal implant in patients with macular edema due to retinal vein
43 43 occlusion. *Ophthalmology* 2010; 117(6):1134-1146.
- 44
45 44 (12) Cunningham MA, Edelman JL, Kaushal S. Intravitreal steroids for macular edema: the past,
46 45 the present, and the future. *Surv Ophthalmol* 2008; 53(2):139-149.
- 46
47 46 (13) Miller JW, Le CJ, Strauss EC, et al. Vascular endothelial growth factor A in intraocular
48 47 vascular disease. *Ophthalmology* 2013; 120(1):106-114.
- 48
49 48 (14) Ford JA, Lois N, Royle P, et al. Current treatments in diabetic macular oedema: systematic
50 49 review and meta-analysis. *BMJ Open* 2013; 3(3).
- 50
51 50 (15) Shyangdan D, Cummins E, Lois N, et al. Dexamethasone implants in the treatment of
52 51 macular oedema due to retinal vein occlusion: a single technology appraisal.

- 1
2
3 52 <http://www.nice.org.uk/nicemedia/live/13037/52883/52883.pdf> . 2010. Aberdeen HTA
4 53 Group.
5 54
- 6 55 (16) Higgins J, Altman D, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk
7 56 of bias in randomised trials. *British Medical Journal* 2011; 343:d5928.
- 8
9 57 (17) Haller JA, Bandello F, Belfort R, Jr., et al. Dexamethasone intravitreal implant in patients
10 58 with macular edema related to branch or central retinal vein occlusion twelve-month
11 59 study results. *Ophthalmology* 2011; 118(12):2453-2460.
- 12
13 60 (18) Yeh WS, Haller JA, Lanzetta P, et al. Effect of the duration of macular edema on clinical
14 61 outcomes in retinal vein occlusion treated with dexamethasone intravitreal implant.
15 62 *Ophthalmology* 2012; 119(6):1190-1198.
- 16
17 63 (19) Bhavsar AR, Ip MS, Glassman AR, DRCRnet and the SCORE Study Groups. The risk of
18 64 endophthalmitis following intravitreal triamcinolone injection in the DRCRnet and SCORE
19 65 clinical trials. *American Journal of Ophthalmology* 2007; 144(3):454-456.
- 20
21 66 (20) Blodi BA, Domalpally A, Scott IU, et al. Standard Care vs Corticosteroid for Retinal Vein
22 67 Occlusion (SCORE) Study system for evaluation of stereoscopic color fundus photographs
23 68 and fluorescein angiograms: SCORE Study Report 9. *Archives of Ophthalmology* 2010;
24 69 128(9):1140-1145.
- 25
26 70 (21) Chan CK, Ip MS, VanVeldhuisen PC, I. et al. SCORE Study report #11: incidences of
27 71 neovascular events in eyes with retinal vein occlusion. *Ophthalmology* 2011; 118(7):1364-
28 72 1372.
- 29
30 73 (22) Ip M, Oden N, VanVeldhuisen P, et al. The Standard Care vs. Corticosteroid for Retinal Vein
31 74 Occlusion Study: Design and Baseline Characteristics. *American Academy of*
32 75 *Ophthalmology* 2008;260.
- 33
34 76 (23) Ip MS, Scott IU, VanVeldhuisen PC, et al. A randomized trial comparing the efficacy and
35 77 safety of intravitreal triamcinolone with observation to treat vision loss associated with
36 78 macular edema secondary to central retinal vein occlusion: the Standard Care vs
37 79 Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5. *Archives of*
38 80 *Ophthalmology* 2009; 127(9):1101-1114.
- 39
40 81 (24) Ip MS, Oden NL, Scott IU, et al. SCORE Study report 3: study design and baseline
41 82 characteristics. *Ophthalmology* 2009; 116(9):1770-1777.
- 42
43 83 (25) Myers D, Blodi B, Ip M, et al. Reading Center Evaluation of OCT Images From Patients
44 84 Enrolled in the Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE) Study.
45 85 *IOVS* 2006; 47:ARVO.
- 46
47 86 (26) Oden NL, Veldhuisen PC, Scott IU, et al. Temporal Variability of OCT in Retinal Vein
48 87 Occlusion Participants in the SCORE Study. *IOVS* 2007; 48:ARVO.
- 49
50 88 (27) Scott IU, VanVeldhuisen PC, Oden NL, et al. SCORE Study report 1: baseline associations
51 89 between central retinal thickness and visual acuity in patients with retinal vein occlusion.
52 90 *Ophthalmology* 2009; 116(3):504-512.
- 53
54
55
56
57
58
59
60

- 1
2
3 91 (28) Scott IU, Blodi BA, Ip MS, et al. SCORE Study Report 2: Interobserver agreement between
4 92 investigator and reading center classification of retinal vein occlusion type. *Ophthalmology*
5 93 2009; 116(4):756-761.
6
7 94 (29) Scott IU, Oden NL, VanVeldhuisen PC, et al. SCORE Study Report 7: incidence of intravitreal
8 95 silicone oil droplets associated with staked-on vs luer cone syringe design. *American*
9 96 *Journal of Ophthalmology* 2009; 148(5):725-732.
10
11 97 (30) Scott IU, VanVeldhuisen PC, Oden NL, et al. Baseline predictors of visual acuity and retinal
12 98 thickness outcomes in patients with retinal vein occlusion: Standard Care Versus
13 99 COrticosteroid for REtinal Vein Occlusion Study report 10. *Ophthalmology* 2011;
14 100 118(2):345-352.
15
16
17 101 (31) Scott IU, VanVeldhuisen PC, Oden NL, et al. Baseline characteristics and response to
18 102 treatment of participants with hemiretinal compared with branch retinal or central retinal
19 103 vein occlusion in the Standard Care vs COrticosteroid for REtinal Vein Occlusion (SCORE)
20 104 study: SCORE Study Report 14. *Archives of Ophthalmology* 2012; 130(12):1517-1524.
21
22 105 (32) Warren K, Blodi BA, Oden N, Veldhuisen P, Scott IU, Ip M. Reading Center Evaluation of
23 106 Baseline Retinal Images in the Standard Care vs. Corticosteroid for Retinal Vein Occlusion
24 107 (SCORE) Study. *Iovs* 2008;ARVO.
25
26 108 (33) Aggermann T, Brunner S, Krebs I, et al. A prospective, randomised, multicenter trial for
27 109 surgical treatment of central retinal vein occlusion: results of the Radial Optic Neurotomy
28 110 for Central Vein Occlusion (ROVO) study group. *Graefes Arch Clin Exp Ophthalmol* 2013;
29 111 251(4):1065-1072.
30
31 112 (34) Boyer D, Heier J, Brown DM, et al. Vascular endothelial growth factor Trap-Eye for macular
32 113 edema secondary to central retinal vein occlusion: six-month results of the phase 3
33 114 COPERNICUS study. *Ophthalmology* 2012; 119(5):1024-1032.
34
35 115 (35) Brown DM, Heier JS, Clark WL, et al. Intravitreal aflibercept injection for macular edema
36 116 secondary to central retinal vein occlusion: 1-Year Results From the Phase 3 COPERNICUS
37 117 Study. *American Journal of Ophthalmology* 2013; 155(3):429-437.
38
39 118 (36) Gillies M. Intravitreal vegf trap-eye in central retinal vein occlusion: Results of the phase 3
40 119 copernicus and galileo studies. *Clinical and Experimental Ophthalmology* 2012; 40:44.
41
42 120 (37) Holz FG, Roeder J, Ogura Y, et al. VEGF Trap-Eye for macular oedema secondary to central
43 121 retinal vein occlusion: 6-month results of the phase III GALILEO study. *British Journal of*
44 122 *Ophthalmology* 2013; 97(3):278-284.
45
46 123 (38) Ciulla TA. Treatment of Macular Edema Following Central Retinal Vein Occlusion With
47 124 Pegaptanib Sodium (Macugen): A One-Year Study. *American Academy of Ophthalmology*
48 125 2007;199.
49
50 126 (39) Csaky KG. Pegaptanib (Macugen) for Macular Edema in Central Retinal Vein Occlusion:
51 127 Early OCT Results and Effect of Therapy Reinitiation. *American Academy of Ophthalmology*
52 128 2007;269.
53
54 129 (40) Patel SS. Pegaptanib Sodium for the Treatment of Macular Edema Following Central
55 130 Retinal Vein Occlusion (CRVO): Anatomical Outcomes. *Iovs* 2007; 48:ARVO.
56
57
58
59
60

- 1
2
3 131 (41) Wells JA. Pegaptanib Sodium for Treatment of Macular Edema Secondary to Central
4 132 Retinal Vein Occlusion (CRVO). *Iovs* 2006; 47:ARVO.
- 5
6 133 (42) Wells JA. Safety and Efficacy of Pegaptanib Sodium in Treating Macular Edema Secondary
7 134 to Central Retinal Vein Occlusion. *American Academy of Ophthalmology* 2006;288.
- 8
9 135 (43) Wells JA, Wroblewski JJ. Pegaptanib Sodium for the Treatment of Macular Edema
10 136 Following Central Retinal Vein Occlusion (CRVO): Functional Outcomes. *Iovs* 2007;
11 137 48:ARVO.
- 12
13 138 (44) Wroblewski JJ, Wells JA, III, Adamis AP, et al. Pegaptanib sodium for macular edema
14 139 secondary to central retinal vein occlusion. *Archives of Ophthalmology* 2009; 127(4):374-
15 140 380.
- 16
17 141 (45) Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for
18 142 macular edema following central retinal vein occlusion: twelve-month outcomes of a
19 143 phase III study. *Ophthalmology* 2011; 118(10):2041-2049.
- 20
21 144 (46) Heier JS, Campochiaro PA, Yau L, et al. Ranibizumab for macular edema due to retinal vein
22 145 occlusions: long-term follow-up in the HORIZON trial. *Ophthalmology* 2012; 119(4):802-
23 146 809.
- 24
25 147 (47) Epstein D, Algvere P, Von WG, et al. Long-term benefit from bevacizumab for macular
26 148 edema in central retinal vein occlusion: 12-month results of a prospective study. *Acta*
27 149 *Ophthalmologica* 2012; 90:48.
- 28
29 150 (48) Epstein DL, Algvere PV, Von WG, et al. Benefit from bevacizumab for macular edema in
30 151 central retinal vein occlusion: twelve-month results of a prospective, randomized study.
31 152 *Ophthalmology* 2012; 119(12):2587-2591.
- 32
33 153 (49) Epstein DL, Algvere PV, Von WG, et al. Bevacizumab for macular edema in central retinal
34 154 vein occlusion: a prospective, randomized, double-masked clinical study. *Ophthalmology*
35 155 2012; 119(6):1184-1189.
- 36
37 156 (50) Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular
38 157 age-related macular degeneration. *N Engl J Med* 2011; 364(20):1897-1908.
- 39
40 158 (51) Campbell RJ, Gill SS, Bronskill SE, et al. Adverse events with intravitreal injection of
41 159 vascular endothelial growth factor inhibitors: nested case-control study. *BMJ* 2012;
42 160 345:e4203.
- 43
44 161 (52) Curtis LH, Hammill BG, Schulman KA, et al. Risks of mortality, myocardial infarction,
45 162 bleeding, and stroke associated with therapies for age-related macular degeneration.
46 163 *Archives of Ophthalmology* 2010; 128(10):1273-1279.
- 47
48 164 (53) Hwang DJ, Kim YW, Woo SJ, et al. Comparison of systemic adverse events associated with
49 165 intravitreal anti-VEGF injection: ranibizumab versus bevacizumab. *J Korean Med Sci* 2012;
50 166 27(12):1580-1585.
- 51
52 167 (54) Sharma S, Johnson D, Abouammoh M, et al. Rate of serious adverse effects in a series of
53 168 bevacizumab and ranibizumab injections. *Can J Ophthalmol* 2012; 47(3):275-279.
- 54
55
56
57
58
59
60

- 1
2
3 169 (55) Micieli JA, Micieli A, Smith AF. Identifying systemic safety signals following intravitreal
4 170 bevacizumab: systematic review of the literature and the Canadian Adverse Drug Reaction
5 171 Database. *Can J Ophthalmol* 2010; 45(3):231-238.
6
7 172 (56) Choi DY, Ortube MC, McCannel CA, et al. Sustained elevated intraocular pressures after
8 173 intravitreal injection of bevacizumab, ranibizumab, and pegaptanib. *Retina* 2011;
9 174 31(6):1028-1035.
10
11 175 (57) Good TJ, Kimura AE, Mandava N, et al. Sustained elevation of intraocular pressure after
12 176 intravitreal injections of anti-VEGF agents. *Br J Ophthalmol* 2011; 95(8):1111-1114.
13
14 177 (58) Chakravarthy U, Harding SP, Rogers CA, et al. Ranibizumab versus bevacizumab to treat
15 178 neovascular age-related macular degeneration: one-year findings from the IVAN
16 179 randomized trial. *Ophthalmology* 2012; 119(7):1399-1411.
17
18 180 (59) Ford JA, Elders A, Shyangdan D, et al. The relative clinical effectiveness of ranibizumab and
19 181 bevacizumab in diabetic macular oedema: an indirect comparison in a systematic review.
20 182 *BMJ* 2012; 345:e5182.
21
22 183 (60) Stewart MW. Aflibercept (VEGF Trap-eye): the newest anti-VEGF drug. *Br J Ophthalmol*
23 184 2012; 96(9):1157-1158.
24
25 185 (61) Braithwaite T, Nanji AA, Greenberg PB. Anti-vascular endothelial growth factor for macular
26 186 edema secondary to central retinal vein occlusion. *Cochrane Database Syst Rev*
27 187 2010;(10):CD007325.
28
29 188 (62) Gewaily D, Greenberg PB. Intravitreal steroids versus observation for macular edema
30 189 secondary to central retinal vein occlusion. *Cochrane Database Syst Rev*
31 190 2009;(1):CD007324.
32
33 191 (63) Lazo-Langner A, Hawel J, Ageno W, et al. Low molecular weight heparin for the treatment
34 192 of retinal vein occlusion: a systematic review and meta-analysis of randomized trials.
35 193 *Haematologica* 2010; 95(9):1587-1593.
36
37 194 (64) Squizzato A, Manfredi E, Bozzato S, et al. Antithrombotic and fibrinolytic drugs for retinal
38 195 vein occlusion: a systematic review and a call for action. *Thromb Haemost* 2010;
39 196 103(2):271-276.
40 197
41 198 (65) Pielen A, Feltgen N, Isserstedt C, et al. Efficacy and safety of intravitreal Therapy in
42 199 macular edema due to branch and central retinal vein occlusion: a systematic review. *PLoS*
43 200 *One* 2013; DOI: 10.1371/journal.pone.0078538
44 201
45 202
46 203
47
48 204
49 205
50 206
51 207
52
53
54
55
56
57
58
59
60

1
2
3 208
4
5 209
6
7 210
8
9 211
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3 **Treatments for macular oedema following central retinal vein occlusion:**
4 **systematic review**
5
6
7

8
9 **Authors**

10 John A. Ford, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich, UK
11 Christine Clar, Warwick Evidence, University of Warwick, Coventry, UK
12 Noemi Lois, Centre for Vision and Vascular Science, Queen's University, Belfast, UK
13 Samantha Barton, BMJ Technology Assessment Group, London, UK
14 Sian Thomas, Warwick Evidence, University of Warwick, Coventry, UK
15 Rachel Court, Warwick Evidence, University of Warwick, Coventry, UK
16 Deepson Shyangdan, Warwick Evidence, University of Warwick, Coventry, UK
17 Norman Waugh, Division of Health Sciences, Medical School, University of Warwick, Coventry, UK
18
19
20
21
22
23
24

25 **Corresponding author**

26 John Ford
27 Norwich Medical School
28 Faculty of Medicine and Health Sciences
29 University of East Anglia
30 Chancellors Drive
31 Norwich, NR4 7TJ
32
33
34
35
36

37 **Protocol:** Not published
38
39

40 **Words:** 5750 words
41

42 **Key words:** central retinal vein occlusion, aflibercept, ranibizumab, bevacizumab, dexamethasone,
43 pegaptanib, triamcinolone, systematic review, anti-VEGF, macular oedema
44
45
46
47

48 **Disclosure**

49 No additional data available.
50
51
52
53
54
55
56
57
58
59
60

Abstract

Objectives

To review systematically the randomised controlled trial (RCT) evidence for treatment of macular oedema due to central retinal vein occlusion (CRVO).

Data sources

MEDLINE, EMBASE, CDSR, DARE, HTA, NHSEED, CENTRAL and meeting abstracts (January 2005 to March 2013).

Study eligibility criteria, participants and interventions

RCTs with at least 12 months' follow-up assessing pharmacological treatments for CRVO were included with no language restrictions.

Study appraisal and synthesis methods

Two authors screened titles and abstracts and conducted data extracted and Cochrane risk of bias assessment. Meta-analysis was not possible due to lack of comparable studies.

Results

Eight studies (35 articles, 1714 eyes) were included, assessing aflibercept (n=2), triamcinolone (n=2), bevacizumab (n=1), pegaptanib (n=1), dexamethasone (n=1) and ranibizumab (n=1). In general, bevacizumab, ranibizumab, aflibercept and triamcinolone resulted in clinically significant increases in the proportion of participants with an improvement in visual acuity of ≥ 15 letters, with 40-60% gaining ≥ 15 letters on active drugs, compared to 12-28% with sham. Results for pegaptanib and dexamethasone were mixed. Steroids were associated with cataract formation and increased intra-ocular pressure. No overall increase in adverse events was found with bevacizumab, ranibizumab, aflibercept or pegaptanib compared to control. Quality of life was poorly reported. All studies had a low or unclear risk of bias.

Limitations

All studies evaluated a relatively short primary follow-up (1 year or less). Most had an unmasked extension phase. There was no head-to-head evidence. The majority of participants included had non-ischaemic CRVO.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Conclusions and implications of key findings

Bevacizumab, ranibizumab, aflibercept and triamcinolone appear to be effective in treating macular oedema secondary to CRVO. Long-term data on effectiveness and safety are needed. Head-to-head trials and research to identify “responders” is needed to help clinicians make the right choices for their patients. Research aimed to improve sight in people with ischaemic CRVO is required.

For peer review only

Article summary

Article focus

To review the clinical effectiveness of pharmacological treatments for central retinal vein occlusion.

Key messages

Bevacizumab, ranibizumab, aflibercept and triamcinolone have demonstrated good short-term clinical effectiveness in randomised controlled trials for the treatment of macular oedema secondary to central retinal vein occlusion.

Dexamethasone and pegaptanib have shown mixed results.

Strengths and limitations of this study

A robust systematic review method was used which only included randomised controlled trials.

There were no head-to-head trials and there was a lack of long-term data on both effectiveness and safety.

Introduction

Central retinal vein occlusion (CRVO) is a vascular disorder of the retina with often catastrophic consequences to vision and quality of life.^{1;2} The incidence of CRVO increases with age; most individuals affected are 50 years of age or older.³ It has been estimated that there are around 80 new cases of CRVO per million population per year.^{4;5} Although CRVO most commonly affects one eye, in around 10% of patients the disease affects both eyes.² Approximately 20% of patients with CRVO will develop large areas of retinal non-perfusion (ischaemia).⁶ Furthermore, a small proportion (around 8%) of patients with non-ischaemic CRVO may convert into the ischaemic type during follow-up.⁶ Retinal ischaemia may lead to the development of neovascularisation in the retina, iris or anterior chamber angle. Complications of neovascularisation include vitreous haemorrhage and neovascular glaucoma.⁶ Currently there is no treatment for ischaemic CRVO other than that aimed at ameliorating the severity of complications, with treatments such as panretinal photocoagulation. Even with the use of current therapies, some eyes with ischaemic CRVO end up blind and painful and, ultimately, enucleation (removal of the eye) is necessary to provide comfort to patients.

Not all people with CRVO will require treatment and macular oedema will resolve in about a third of those with non-ischaemic CRVO.^{2;7} However most will need treatment and the number of options has increased in recent years. Laser photocoagulation has been for many years the standard therapy for patients with macular oedema secondary to branch retinal vein obstruction (BRVO).⁸ However, laser treatment was not found to be beneficial to those with macular oedema secondary to CRVO;⁹ for these patients, no therapeutic modalities could be offered. Recently, several studies have demonstrated the benefit of anti-vascular endothelial growth factor (VEGF) therapies and steroids for the management of patients with macular oedema secondary to CRVO.^{10;11} Steroids, such as triamcinolone and dexamethasone, have anti-inflammatory and anti-proliferative attributes (as well as some anti-VEGF effects) and therefore are primarily effective by reducing the oedema of the macula.¹² Anti-VEGF treatments, such as bevacizumab, ranibizumab, aflibercept and pegaptanib, inhibit vascular endothelial growth factor A. In CRVO there is an increase in vascular endothelial growth factor A which leads to neovascularization and oedema.¹³ In the UK, NICE has approved dexamethasone (in the long-acting form, Ozurdex) and ranibizumab (Lucentis) and an appraisal of aflibercept is currently underway. Bevacizumab is also used, but is not licensed for use in the eye; however this is because the manufacturer has never sought a licence, preferring to market ranibizumab. Triamcinolone has also been used off-licence.

1
2
3 An up-to-date review incorporating all drug treatments for macular oedema secondary to CRVO is
4 needed. The purpose of this study is to review systematically the randomised controlled evidence
5 for drug treatments of macular oedema secondary to CRVO.
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Methods

A systematic review was conducted. The following databases were searched: MEDLINE, MEDLINE In-process, EMBASE (all via OVID); CDSR, DARE, HTA, NHSEED, CENTRAL (all via The Cochrane Library); Science Citation Index and Conference Proceedings Citation Index-Science (via Web of Knowledge). In addition to the bibliographic database searching, supplementary searches were undertaken to look for recent and unpublished studies in the WHO International Clinical Trials Registry Platform and ophthalmology conference websites (American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology from 2010 to 2012).

Search strategy

An iterative procedure was used to develop two search strategies with input from previous systematic reviews.^{14;15} The first search strategy was designed to retrieve articles reporting RCTs or systematic reviews about CRVO published from 2005 onwards (the publication date of the first RCT on triamcinolone in Medline). Terms for retinal vein occlusion were included to ensure identification of articles in which both BRVO and CRVO were covered, but were reported separately. The second strategy focussed on retrieving articles where adverse events of relevant pharmacological treatments for CRVO were reported. This second search was limited by condition (age-related macular degeneration (AMD) or RVO), study type (RCTs, SRs or observational studies) and date (published from 2010 onwards). Searches were conducted in March 2013. The strategies used in each database are provided in appendix 1. Auto alerts of searches were set up to capture relevant articles published after the dates of the searches.

Reference lists from the included studies and identified systematic reviews were screened.

Inclusion and exclusion criteria

RCTs were used to assess the clinical effectiveness and adverse events.

Only RCTs examining pharmacological treatment compared with laser treatment, observation, placebo (sham injection) or another pharmacological intervention with at least 12 months follow-up were included. Comparisons of different doses of drugs were not included unless there was an additional comparator group as defined above. Studies including CRVO and BRVO were included

1
2
3 providing participants with CRVO were reported as a subgroup. Studies assessing treatments aimed
4 at restoring circulation to the occluded vein shortly after onset (<30 days) were excluded. There
5 were no language restrictions.
6
7
8
9

10 *Outcomes*

11
12 The primary outcome was visual acuity measured as mean change in best corrected visual acuity
13 (BCVA) or as proportion of patients improving by 15 ETDRS (Early Treatment for Diabetic
14 Retinopathy Study) letters or more. Secondary outcomes included mean change in macular thickness
15 using optical coherence tomography (OCT), quality of life and adverse events.
16
17
18
19
20

21 *Screening and data extraction*

22
23 Search results were screened independently by two authors (CC, JF and ST). Differences were
24 resolved through discussion or by consulting a third author (JF). Data were extracted by one author
25 (CC and DS) and checked by a second (ST, CC). Data extraction included inclusion/exclusion criteria,
26 baseline demographics, mean change in BCVA, proportion of patients with 15 letters improvement,
27 central retinal thickness (CRT) and adverse events. Risk of bias was assessed by two reviewers using
28 the Cochrane risk of bias tool.¹⁶
29
30
31
32
33
34
35

36 Meta-analysis was not possible because of a lack of comparable studies.
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Results

Search results

The study flow is shown in figure 1. The electronic searches yielded 518 records. 475 were eliminated based on information in the titles and abstract. The full text of the remaining 43 records was checked, and a further eight were eliminated. Reasons for exclusion included the trial being a commentary rather than an RCT, the study having no relevant comparison group (dose ranging only), the participants did not have macular oedema secondary to CRVO, or the interventions being ineligible (non-pharmacological). The remaining 35 records (including conference abstracts) reported on eight RCTs of six different pharmacological agents, and these were included in the analysis. The Geneva study (2010)^{11,17,18} technically consists of two RCTs, but as these were analysed and reported together, it was counted as one RCT in this analysis.

We also identified three relevant ongoing trials, one investigating minocycline (<http://clinicaltrials.gov/ct2/show/study/NCT01468844>), one investigating a combination of bevacizumab and triamcinolone (<http://clinicaltrials.gov/show/NCT00566761>), and one investigating ranibizumab (<http://clinicaltrials.gov/show/NCT01123564>).

Study characteristics

Detailed study characteristics of the included studies are shown in table 1.

Study design

Of the eight included RCTs, six were described as double-blind and seven were sham-controlled. All but one were multicentre. Only one was not funded by industry. Four trials were international trials, two came from the USA, and one each from Austria and Sweden. Six of the trials measured primary end-points at around six months (24 to 30 weeks), whereas two measured primary end-points at 12 months. Five studies reported follow-up data for up to 12 months, and two reported data for follow-up periods of up to two years.

Participants

The trials randomised a total of 1714 eyes (one eye per person). The number of eyes per study ranged between 60 and 437. Follow-up at the primary end-point ranged from 77 to 98% (generally over 90% in the intervention groups). The participants had a mean age of between 59.0 and 70.5

1
2
3 years, and between 36 and 49% were female. Only two studies reported mean duration of macular
4 oedema (4.3 and 4.9 months). Five studies reported mean time since CRVO diagnosis (range 2.4 to
5 2.9 months). Mean baseline BCVA was between 44 and 52.5 ETDRS letters, baseline CRT was
6 between 569 and 721 μm . In most trials, the focus was on macular oedema secondary to CRVO only,
7 but in the Geneva trial macular oedema secondary to BRVO and CRVO was included and only limited
8 data were available on the CRVO-only group.
9
10

11 12 13 *Interventions*

14
15 The Geneva trial (2010 ff.)^{11;17;18} compared a 0.35 mg (n=136) and a 0.7 mg dexamethasone (n=154)
16 intravitreal implant with sham treatment (n=147). After the initial 6 month study period, patients
17 could enter a 6 month open label extension, where they received a 0.7 mg dexamethasone
18 intravitreal implant.
19
20
21

22
23 The SCORE trial (2009 ff.)¹⁹⁻³² compared intravitreal injections of 1 or 4 mg of triamcinolone (~2
24 injections over 12 months, n= 92 and 91 for 1 and 4 mg respectively) with an observation group
25 (n=88). Two forms of triamcinolone have been used in trials exist; the SCORE trial used Trivaris, rather
26 than Kenalog. Trivaris is no longer available t used as much because its manufacturer has promoted
27 an alternative steroid (dexamethasone). The ROVO trial (2013)³³ compared a single intravitreal
28 injection of 4 mg of triamcinolone (over 12 months, n=25) with radial optic neurotomy (n=38) or
29 sham injection (n=20).
30
31
32
33
34

35
36 In the COPERNICUS trial (2012)^{34;35}, intravitreal injections of 2 mg of aflibercept (n=114) were given
37 every 4 weeks over 24 weeks to the intervention group and the comparison group received a sham
38 injection (n=75). During weeks 24 to 52, patients in both groups received aflibercept if they met
39 protocol-specified retreatment criteria, and received a sham injection if retreatment was not
40 indicated (3.9 standard error 0.3 injections in the sham group and 2.7 standard error 0.2 injections in
41 the aflibercept group); after the first year, patients continued in a one-year extension phase with as
42 needed dosing. In the GALILEO trial (2012)^{36;37}, intervention patients also received intravitreal
43 injections of 2 mg of aflibercept (n=103) every 4 weeks over 24 weeks, while the comparison group
44 was given sham injections (n=71). During weeks 24 to 52, patients remained in their original
45 treatment groups but received their allocated treatment as needed; beginning from week 52 to
46 week 76, both groups received the study drug every 8 weeks.
47
48
49
50
51
52

53
54 In a trial by Wroblewski and colleagues (2009)³⁸⁻⁴⁴, patients received 0.3 or 1 mg intravitreal
55 injections of pegaptanib sodium every 6 weeks for 24 weeks (n=33 and 33), compared with a sham
56 injection group (n=32). Patients were followed up to 52 weeks.
57
58
59
60

1
2
3 The CRUISE trial (2010 ff.)^{10;45;46} compared monthly injections of 0.3 or 0.5 mg of ranibizumab (n=132
4 and 130) over 6 months with sham injection (n=130). During months 6 to 12, all patients could
5 receive intraocular ranibizumab (previously assigned dose or 0.5 mg for the sham group) if they met
6 prespecified functional and anatomic criteria; after 12 months' follow-up patients could continue in
7 the HORIZON trial for another 12 months, where they were eligible to receive intravitreal injections
8 of 0.5 mg ranibizumab if they fulfilled prespecified criteria.
9

10
11
12
13 Epstein and colleagues (2012)⁴⁷⁻⁴⁹ conducted an RCT in which they compared patients receiving four
14 intravitreal injections of 1.25 mg of bevacizumab (n=30) over 6 months with patients receiving sham
15 injection (n=30). From 6 to 12 months, all patients received intravitreal bevacizumab injections every
16 6 weeks.
17
18
19

20
21 *Outcomes.* The primary endpoint of all but one study was the proportion with a gain of 15 or more
22 ETDRS letters. The primary endpoint of the remaining study was mean change in BCVA. Studies also
23 reported gains or losses of ETDRS letters at various cut-off points, absolute BCVA, CRT, and safety
24 parameters. The COPERNICUS, the GALILEO and the CRUISE studies also measured vision-related
25 quality of life (National Eye Institute Visual Functioning Questionnaire, NEI-VFQ).^{10;34-37;45;46} EQ5D was
26 also used in GALILEO.
27
28
29

30
31 *Ongoing studies.* Of the ongoing trials, the first (clinicaltrials.gov NCT01468844) is a 24 month
32 double-blind RCT from the USA. It set out to test the safety and effectiveness of minocycline as a
33 treatment for CRVO in around 20 patients with macular oedema secondary to CRVO. Both groups
34 received monthly intravitreal bevacizumab injections over three months (and afterwards as needed),
35 and the intervention group also received 100 mg oral minocycline twice daily over 24 months. The
36 second trial (clinicaltrials.gov NCT00566761) is an open-label RCT from Mexico in only around 10
37 patients assessing whether combined treatment with bevacizumab and triamcinolone is more
38 effective than bevacizumab alone. The combination group received 2.5 mg of bevacizumab plus 4
39 mg of triamcinolone as a first dose and then two doses of bevacizumab alone at monthly intervals,
40 while the monotherapy group received three monthly doses of 2.5 mg bevacizumab alone. Follow-
41 up will be 12 months. A third RCT from Hungary compares monthly injections of ranibizumab for
42 three months (and as needed thereafter) with Argon laser treatment in around 40 patients with
43 macular oedema secondary to CRVO. Follow-up will also be 12 months. The primary endpoint in all
44 studies is BCVA over 12 months.
45
46
47
48
49
50
51
52
53
54

55
56
57 *Risk of bias*
58
59
60

1
2
3 Details of risk of bias assessment are shown in Table 3.
4

5 Most studies (except GALILEO (2012) and Epstein 2012)^{36;37;47-49} adequately described the generation
6 of the allocation sequence, but only half the studies gave enough details to confirm adequate
7 allocation concealment. Most studies (unclear in the ROVO 2013 study)³³ used at least partial
8 masking, and most studies appeared to have had masking of outcome assessment. Intention-to-treat
9 analysis was used in all studies. Where reported separately for comparison groups, losses to follow-
10 up tended to be slightly higher for the control groups than the interventions groups (79 to 88.5%
11 follow-up in the control groups and 90 to 98% in the intervention groups). All studies appeared to
12 have been free of selective reporting. Most studies included a power analysis (not reported for the
13 CRUISE study)^{10;45;46}, but in two cases (the SCORE and the ROVO studies)¹⁹⁻³³ the numbers
14 randomised were considerably below the numbers indicated in the power calculations. As far as
15 reported, there were no significant differences between comparison groups in baseline
16 characteristics.
17
18
19
20
21
22
23
24
25
26
27

28 *Clinical effectiveness*

29
30 Detailed study results can be found in Table 2.
31

32
33 *Visual acuity.* Figure 2 shows the primary endpoint in most studies, which was the proportion of
34 participants with a gain of 15 or more ETDRS letters. As there were no significant differences in
35 visual acuity results between groups using different dosages of the given pharmacological treatment,
36 intervention groups were combined for the sake of the plot.
37
38

39
40 In the Geneva trial (2010 ff.)^{11;17;18}, treatment of macular oedema secondary to CRVO with a 0.7 mg
41 intravitreal dexamethasone implant resulted in a 0.1 letter gain in BCVA compared to a loss of 1.8 in
42 the sham group ($p < 0.001$). The difference persisted in the extension period where all patients
43 received the 0.7 mg dexamethasone implant. However, there was no significant difference in the
44 proportion of patients gaining or losing 15 letters at either 6 or 12 months (0.35 or 0.7 mg
45 dexamethasone). This may reflect the timing of peak effect at 90 days with dexamethasone.
46
47
48
49

50
51 In the SCORE trial (2009 ff.)¹⁹⁻³², patients in the triamcinolone groups lost significantly fewer ETDRS
52 letters (triamcinolone 1mg 1.2 letters loss, 4mg 1.2 letters loss and observation 12.1 letters loss)
53 over both 12 and 24 months than patients in the observation group. The proportion of patients
54 gaining 15 letters or more was also significantly larger in the intervention groups at 12 and 24
55 months (25.6% compared with 6.8% and 31% compared with 9%, respectively). The proportion of
56
57
58
59
60

1
2
3 patients receiving triamcinolone and losing 15 letters or more was smaller (25.6%) than in the
4 observation group (43.8%), but this difference was not statistically significant ($p=0.06$).
5
6

7 There was some overall improvement in BCVA in both intervention groups at 12 months in the ROVO
8 trial (2013)³³, (triamcinolone 20%, radial optic neurotomy 47% and sham 10%) however it was
9 unclear whether there were any statistically significant differences between the 4 mg triamcinolone,
10 the radial optic neurotomy, or the sham group. However, there were significantly more patients with
11 an improvement of more than or equal to 15 letters in the neurotomy group than in the sham group
12 (47% versus 10%), but no significant difference to sham after one dose of triamcinolone.
13
14
15
16

17 In both the COPERNICUS (2012)^{34;35} and GALILEO (2012)^{36;37} trials patients in the aflibercept group had
18 a significant improvement in BCVA at 6 months of 18 and 17.3 letters (compared to 4 letters loss and
19 3.3 letter gain in sham groups respectively), and this was maintained at 12 months and was
20 significantly greater than the improvements in the sham groups. This was paralleled by a significantly
21 greater proportion of patients (56.1% compared with 12.3% and 60.2% compared with 22.1%,
22 respectively) gaining 15 letters or more. Patients treated sooner after diagnosis (less than versus
23 more than two months) seemed to benefit more (in terms of proportion of patients with 15 letters
24 or more gain) in both trials.
25
26
27
28
29
30

31 The increase in mean change in BCVA with 0.3 mg pegaptanib compared with sham did not reach
32 significance at 30 weeks in the trial by Wroblewski and colleagues (2009)³⁸⁻⁴⁴, but there was a
33 greater increase in BCVA with 1 mg pegaptanib compared with sham (9.9 letter gain compare with
34 3.2 letter loss). These differences were not statistically significant at 52 weeks. There was no
35 significant difference between any of the groups in the proportion of patients gaining 15 letters or
36 more at 30 weeks, but significantly fewer patients in both dosage groups lost 15 letters or more than
37 in the sham group (6% compared with 31%).
38
39
40
41
42

43 In the CRUISE trial (2010 ff.)^{10;45;46}, mean change in BCVA was significantly increased in the
44 ranibizumab groups (no difference between doses) compared with the sham group at both 6 and 12
45 months (12.0 letters gained in the 0.5 mg group compared to 7.6 in the sham group). After the one
46 year extension with ranibizumab as needed in all groups, there was no difference between the doses
47 of ranibizumab at 24 months. The pattern was similar for the proportion of patients gaining 15
48 letters or more.
49
50
51
52

53 In the trial by Epstein and colleagues (2012)⁴⁷⁻⁴⁹, treatment with intravitreal bevacizumab, compared
54 with sham treatment significantly increased mean change in BCVA (14.1 letters gain compared to 2.0
55 letters lost) and the proportion of patients gaining 15 letters or more (60% compared to 20%) at 24
56
57
58
59
60

1
2
3 weeks. This difference was maintained in the extension period, even though both groups had been
4 receiving bevacizumab. Younger patients (<70 years) tended to have better visual outcomes than
5 older patients (>70 years).
6
7

8
9 *Central retinal thickness.* In the Geneva trial (2010 ff.)^{11;17;18}, no significant difference was found in
10 the reduction of CRT after 6 months' treatment in patients with macular oedema secondary to CRVO
11 with the 0.7 mg intravitreal dexamethasone implant (no data given for the 0.35 mg implant)
12 compared with sham.
13
14

15
16 In the SCORE trial (2009 ff.)¹⁹⁻³², CRT decreased in all study groups, but there was no significant
17 difference between groups at either 12 or 24 months. Similarly, there was no clear difference in the
18 proportion of patients achieving a CRT of less than 250 µm. CRT decreased in all comparison groups
19 in the ROVO trial (2013)³³, but there was no significant difference between groups.
20
21

22
23 Both in the COPERNICUS trial (2012)^{34;35} and in the GALILEO trial (2012)^{36;37} there was a significantly
24 greater reduction in CRT at 6 months in the aflibercept group than in the control group. However the
25 significant difference was maintained in the longer term only in the GALILEO trial, where patients
26 continued their assigned treatment up to 12 months. In the COPERNICUS trial, patients in the sham
27 group also received aflibercept in the extension period, which caused a similar decrease in CRT as in
28 the original intervention group.
29
30
31

32
33
34 After 30 weeks of treatment with pegaptanib (Wroblewski and colleagues 2009)³⁸⁻⁴⁴, differences in
35 decrease of CRT versus sham did not reach significance, but at 52 weeks, the decrease in CRT was
36 significantly greater in both the 0.3 mg and the 1 mg pegaptanib groups compared with sham.
37
38

39
40 After treatment with ranibizumab in the CRUISE trial (2010 ff.)^{10;45;46}, a significant reduction in CRT
41 was observed and significantly more patients achieved a CRT of 250 µm or less in the intervention
42 groups (no difference between doses) than in the sham group at 6 months. This difference did not
43 persist at 12 and 24 months because all groups received ranibizumab as needed.
44
45

46
47 In the trial by Epstein and colleagues (2012)⁴⁷⁻⁴⁹, treatment with intravitreal bevacizumab
48 significantly decreased CRT and the proportion of patients with no residual oedema (CRT <300 µm)
49 at 24 weeks, compared with sham treatment. When both groups received bevacizumab in the
50 extension period, similar decreases in CRT and increases in the proportion of patients with no
51 residual oedema were seen.
52
53
54

55
56 *Vision-related quality of life.* Vision-related quality of life (NEI-VFQ25) was significantly higher in the
57 aflibercept group, compared with sham injection, at 6 months in both the COPERNICUS trial (+7.2
58
59
60

1
2
3 compared with +0.8)^{34;35} and the GALILEO trial (+7.5 compared with +3.5)^{36;37}. In the COPERNICUS
4 trial, patients in the sham group who received aflibercept in the extension period had a similar
5 increase in vision-related quality of life as patients in the original intervention group by 12 months.
6
7

8
9 In the CRUISE trial (2010 ff.)^{10;45;46}, vision-related quality of life (NEI-VFQ) was similarly increased in
10 both ranibizumab groups and statistically significantly more than in the sham group at 6 months
11 (+6.2 compared with +2.8). At 12 months, with all groups receiving ranibizumab as needed, the
12 increases were similar in all three groups.
13
14

15
16 *Adverse events.* The 0.7 mg dexamethasone intravitreal implant caused significantly more increased
17 intraocular pressure (IOP) than sham treatment (30.1%, versus 1.4% in the control group) in patients
18 with CRVO in the Geneva trial (2010 ff.)^{11;17;18} (not reported for 0.35 mg). The incidence of cataract
19 was also slightly higher in the dexamethasone group but numbers were small because of the short
20 duration . There were no other differences in adverse events between groups.
21
22
23

24
25 In the triamcinolone group (especially 4 mg, SCORE trial 2009 ff.)¹⁹⁻³², there was a higher increase in
26 IOP, lens opacity onset or progression (at 12 months) and cataract surgery (12 to 24 months) than in
27 the control group. There were no other differences in adverse events between groups. A similar
28 tendency was seen in the ROVO trial (2013)³³.
29
30
31

32 Aflibercept did not appear to increase the incidence of ocular or non-ocular adverse events
33 compared with sham in both the COPERNICUS trial (2012)^{34;35} and the GALILEO trial (2012)^{36;37}.
34
35

36 In the trial by Wroblewski and colleagues (2009)³⁸⁻⁴⁴, adverse events in response to pegaptanib were
37 not reported in detail, but there do not appear to have been any serious ocular or systemic adverse
38 events.
39
40

41
42 After treatment with ranibizumab in the CRUISE trial (2010 ff.)^{10;45;46}, there were no consistent
43 differences in ocular or systemic adverse events between the intervention groups. None of the
44 ocular adverse events appeared to have increased substantially after all patients received
45 ranibizumab up to 24 months.
46
47

48
49 Epstein and colleagues (2012)⁴⁷⁻⁴⁹ did not report adverse events in response to bevacizumab in
50 detail, but the treatment appears not to have caused any serious ocular adverse events over 48
51 weeks.
52
53
54
55
56
57
58
59
60

Discussion

Statement of principal findings

~~Compared to control,~~ [Evidence from good quality RCTs shows that](#) intravitreal steroids and anti-VEGF therapies increase the proportion of patients whose vision improves by 15 or more letters in patients with macular oedema secondary to CRVO. The most effective drugs result in over 60% of patients gaining 15 letters compared to only about 20% of the control groups. [The RCT evidence shows only demonstrates the](#) short-term effectiveness of ranibizumab, bevacizumab, aflibercept and triamcinolone. Results from trials of dexamethasone and pegaptanib were mixed. Long-term evidence is awaited.

Strengths and limitations

A robust systematic review methodology was used. A broad search strategy was implemented, which included not restricting the search strategy with drug terms. Grey literature was searched by screening meeting abstracts from relevant conferences. There were no language restrictions. Two reviewers screened titles and abstracts and conducted data extraction and risk of bias assessment. Risk of bias was assessed using the Cochrane Risk of Bias Tool and was generally judged to be low or unclear. Only studies with one year follow up were included to exclude studies with very short follow-up RCTs were identified for all the new ophthalmological drugs, except for the steroid, fluocinolone.

The main limitation is the short duration of follow-up. The primary outcome for most trials was measured at 6 months, with an extension phase up to 12 months. Hence, it is not known whether the benefit of these treatments will be maintained long-term. Furthermore, potential side effects of these treatments may not be captured in these studies as a result of their short follow-up. Patients and clinicians would like sustained, life-long improvement in visual acuity, but of all included studies only one of them had a follow-up of over 24 months.

The sample size of some studies was small. For example, the evidence for pegaptanib and bevacizumab comes from studies with around 30 participants per arm which substantially increases the risk of a type II error. Only three trials included quality of life data, arguably one of the most important outcomes.

1
2
3 The proportion of participants and severity of ischemia within the trials was not clear. Whilst
4 ischaemia is not mentioned in the inclusion/exclusion criteria of most studies, these participants
5 were unlikely included in these studies, especially if the diagnosis of ischaemic CRVO is based on
6 strict criteria. Furthermore patients were entered into the trials relatively soon after diagnosis (mean
7 4.3 to 4.9 months) and the it is not clear if the effects would be similar in patients who present with
8 long standing disease.
9

10
11
12
13 Another weakness was that patients were not asked at the of trials, what treatment they thought
14 they had received, which would have provided data on the success of masking of allocation.
15

16
17
18 In the case of dexamethasone, the results at six months were not as good as at 90 days, because of
19 the duration of action. Earlier re-treatment, at say 120 days, would have improved results, but many
20 clinicians might be reluctant to repeat injections of dexamethasone implant often because of the
21 large needle size and risk of adverse effects.
22

23 24 25 *Adverse events*

26
27 Results from the included studies clearly demonstrate that steroids (triamcinolone and
28 dexamethasone) are associated with clinically meaningful increases in IOP and cataract progression.
29 Anti-VEGF therapy ocular adverse events reported in the trials were similar in both placebo and
30 intervention arms.
31

32
33
34 There is limited evidence of the safety of these drugs specifically in CRVO, but it would not be
35 unreasonable to look to trials in neovascular age-related macular degeneration (AMD) and diabetic
36 macular oedema (DMO) for safety data, where there is more experience. The CATT trial, which
37 compared bevacizumab with ranibizumab in AMD, suggested that there was a higher incidence (RR
38 1.29 95%CI 1.01 to 1.66) of serious systematic adverse events (primarily hospitalisations) in the
39 bevacizumab arm.⁵⁰ Some have raised concerns about arterial thromboembolic events with
40 bevacizumab, but none of these has been demonstrated in the published literature.⁵¹⁻⁵⁴ Micieli and
41 colleagues (2010) undertook a systematic review of the adverse events associated with
42 bevacizumab. 22 studies were reviewed, representing 12,699 participants.⁵⁵ Adverse events in
43 patients treated with bevacizumab were cerebrovascular events (0.21%), myocardial infarction
44 (0.19%) and increased blood pressure (0.46%). Most of these represent the background burden of
45 disease in patients with advanced eye disease. The proportion of these directly attributable to
46 bevacizumab is likely to be very small. Campbell and colleagues (2012) undertook a nested case-
47 control study of over 7,000 cases and 37,000 controls.⁵¹ Ranibizumab and bevacizumab injection was
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 the exposure and cardiovascular events were the outcome. The authors found that ranibizumab and
4 bevacizumab were not associated with increased cardiovascular events.
5

6
7 Increased IOP has been associated with ranibizumab, bevacizumab and pegaptanib. Sustained
8 increased in IOP has estimated to be 5.5-6.0% with these drugs.^{56;57}
9

10
11 Robust evidence on the long-term safety of aflibercept is awaited.
12

13 14 15 16 *What do these results mean?*

17
18 Until very recently, patients with macular oedema as a result of CRVO could only be offered visual
19 rehabilitation and visual aids in an attempt to help them to deal better with their reduced vision and
20 its implications in their daily activities and quality of life. Their future is brighter now as new options
21 to treat macular oedema have become available. Triamcinolone is likely to be a cost-effective
22 treatment at least in selected groups of patients, such as pseudophakic individuals or those with pre-
23 existing cataracts that may require cataract surgery in the near future. The lack of a commercially
24 available licensed product for intraocular administration may restrict its use in clinical practice.
25
26
27
28

29
30 Some anti-VEGF therapies, including bevacizumab, ranibizumab and aflibercept, have been also
31 shown to be effective in short term studies for the treatment of patients with macular oedema and
32 CRVO. Bevacizumab has the advantage of having a low cost, ~~because it is aliquoted~~, with an
33 apparently similar effect to other anti-VEGF therapies^{50;58;59} but there is some reluctance to use it as
34 it is not licensed for use in the eye. This has been seen in other eye conditions, such as AMD and
35 DMO. Aflibercept, requiring potentially fewer injections than other anti-VEGF agents, could
36 represent an advantage to patients and may relieve pressure on ophthalmology clinics. ~~As more
37 options have become available, ophthalmologists will need to decide, together with their patients,
38 which may be the best treatment option for them based on their visual requirements and life
39 circumstances.~~ Health care systems will need to evaluate the cost-effectiveness of these new
40 treatments and support affordable ones. The National Institute for Health and Care Excellence is
41 currently appraising aflibercept. Policy makers are left in a difficult position because of bevacizumab.
42 It is cheaper than all other drugs⁶⁰ and appears to be as effective, but is unlicensed and unlike
43 ranibizumab and aflibercept does not have evidence from large, well-funded RCTs in CRVO. The use
44 of bevacizumab would result in considerable savings for the NHS.
45
46
47
48
49
50
51
52
53
54

55
56 It is important to note that the evidence of benefit of these new therapies is likely to only apply to
57 patients with non-ischaemic CRVO. Although some patients with ischaemic CRVO were included,
58
59
60

1
2
3 these individuals are likely to have mild ischaemic CRVO. Thus, for patients with established
4 ischaemic CRVO, there are no proven treatments available and further research into this area is very
5 much needed.
6
7
8
9

10
11 *What is the context of these results*
12

13 Earlier systematic reviews identified limited evidence on the clinical effectiveness of treatments. A
14 review by Braithwaite and colleagues (search date August 2010)⁶¹ on anti-VEGF agents identified one
15 RCT^{10;45;46} comparing two doses of ranibizumab and one RCT³⁸⁻⁴⁴ comparing two doses of pegaptanib
16 sodium versus placebo or no treatment. In both RCTs, the higher dose of the anti-VEGF significantly
17 improved BCVA compared with sham injection in the short term (~6 months), but the effects in the
18 longer term were unclear. Braithwaite and colleagues concluded that data from the two RCTs could
19 not be synthesised because ranibizumab and pegaptanib sodium might not be directly comparable.
20 Subsequent RCTs identified in this review also suggest benefit in ocular outcomes in macular
21 oedema secondary to non-ischaemic CRVO for the anti-VEGFs bevacizumab, and aflibercept.^{34-37;47-49}
22
23
24
25
26
27
28

29 Gewaily and Greenberg reviewed the literature on intravitreal corticosteroids (search date
30 November 2008) versus observation in macular oedema secondary to CRVO and identified no
31 relevant RCTs.⁶² Results from two observational studies suggested that triamcinolone acetonide
32 might be beneficial in the treatment of macular oedema secondary to non-ischaemic CRVO.
33 However, as the authors of the review caution because conclusions are primarily drawn from small
34 case series and case reports with short follow up. Results from the SCORE 2009 RCT corroborate the
35 observational studies.¹⁹⁻³² The effects of triamcinolone acetonide in people with non-ischaemic CRVO
36 without associated macular oedema are less clear. Data from four observational studies led Gewaily
37 and Greenberg to conclude that intravitreal corticosteroids are associated with transient anatomical
38 and functional improvements.
39
40
41
42
43
44
45

46 Immediate treatment aimed at relieving the blocked vein and surgical interventions were outwith
47 the remit of this review. Antithrombotics, such as low-molecular weight heparin (LMWH), and
48 fibrinolytics have also been found to benefit visual acuity in retinal vein occlusion with no associated
49 macular oedema. Two systematic reviews^{63;64} identifying the same three RCTs in recent onset (≤ 30
50 days) BRVO or CRVO found that LMWH improved visual acuity compared with aspirin and that the
51 associated benefit was larger in CRVO; only one of the three RCTs included people solely with CRVO.
52 One review⁶⁴ also included one RCT comparing ticlopidine with placebo and two RCTs assessing
53 intravenous fibrinolytic therapy followed by warfarin or aspirin with either haemodilution or no
54
55
56
57
58
59
60

1
2
3 treatment. The authors of the reviews conclude that no definitive recommendations can be made on
4 clinical effectiveness of LMWH in CRVO given the limited evidence available.
5
6

7 Radial optic neurotomy involves the performance of a radial cut using a microvitreal (MVR)
8 blade through the lamina cribrosa, scleral ring and adjacent sclera at a selected point in the optic
9 nerve head with the goal of "decompressing" the scleral outlet (space confined by the scleral ring
10 and containing the lamina cribrosa, the central retinal artery, central retinal vein and the optic
11 nerve. The [SCORE-ROVO](#) trial found radial optic neurotomy to be more effective than sham.
12
13

14
15
16 While this review was being considered for publication, another was published, with differences in
17 scope (BRVO and CRVO) and inclusions (this review is more up to date).⁶⁵ The reviewers found that
18 aflibercept and bevacizumab resulted in greatest gain, followed by ranibizumab and triamcinolone.
19 The overall conclusions in both reviews were similar.
20
21

22 23 *Further research*

24
25 Large adequately powered RCTs comparing ranibizumab, bevacizumab, aflibercept and
26 triamcinolone are needed. Part of the problem is that the US the Food and Drug Administration
27 requires pharmaceutical companies to present data establishing a drug's safety and effectiveness.
28 Whilst this does not specifically require a placebo-controlled trial, it is the most efficient study
29 design for demonstrating effectiveness and safety. Clinicians and researchers are left with placebo-
30 controlled trials demonstrating effectiveness for individual drugs, but a lack of evidence to help
31 them decide which is best for their patients.
32
33

34
35 Given the cost of these treatments and the burden of repeated injections to patients and health care
36 systems, research aiming to predict "responders" would be useful as at present this is done by
37 therapeutic trial. Treatments could then be targeted to patients likely to benefit. Research is also
38 needed on the frequency and sequences of drugs. As other pathogenic pathways besides
39 inflammation and VEGF-mediated pathways may be implicated in the development of macular
40 oedema in patients with CRVO, these should be investigated in an attempt to develop new
41 therapeutic strategies for this condition. Research is also needed into optimum timing of treatment
42 after CRVO. The cost-effectiveness of diagnostic technologies for determining when retreatment is
43 necessary should be examined.
44
45

46
47 We also need better treatments since a significant proportion of patients do not improve with all of
48 these drugs
49
50
51
52

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Future RCTs should include longer term outcomes, as functional results observed at six months or even one year may not necessarily be representative of what is likely to be achieved longer term and, furthermore, potential side effects of treatments, such as retinal atrophy after repeated injections of anti-VEGFs, may not be captured in shorter term studies.

For peer review only

Conclusions

Bevacizumab, ranibizumab, aflibercept and triamcinolone appear to be effective in improving the number of patients who gain 15 letters or more in CRVO. There are mixed results for dexamethasone and pegaptanib. Steroids were associated with cataract progression and increased IOP. Long-term data on effectiveness and safety are needed. Head-to-head trials and research to identify “responders” is needed to help clinicians make the right choices for their patients.

For peer review only

1
2
3 **Acknowledgments:** None
4

5 **Conflict of interest:** None
6

7 **Funding:** This research received no specific grant from any funding agency in the public, commercial
8 or not-for-profit sectors
9

10
11 **Contributions:** NW devised the idea for the review. JF wrote the protocol and all authors
12 contributed to the design of the protocol. RC undertook the literature searches. JF, CC and ST
13 screened titles and abstracts. CC, ST and DS extracted the data. All authors contributed to the
14 interpretation of the results. JF, NL, RC, CC and SB contributed to the first draft of the article. All
15 authors reviewed and commented on the final manuscript.
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1: PRISMA statement

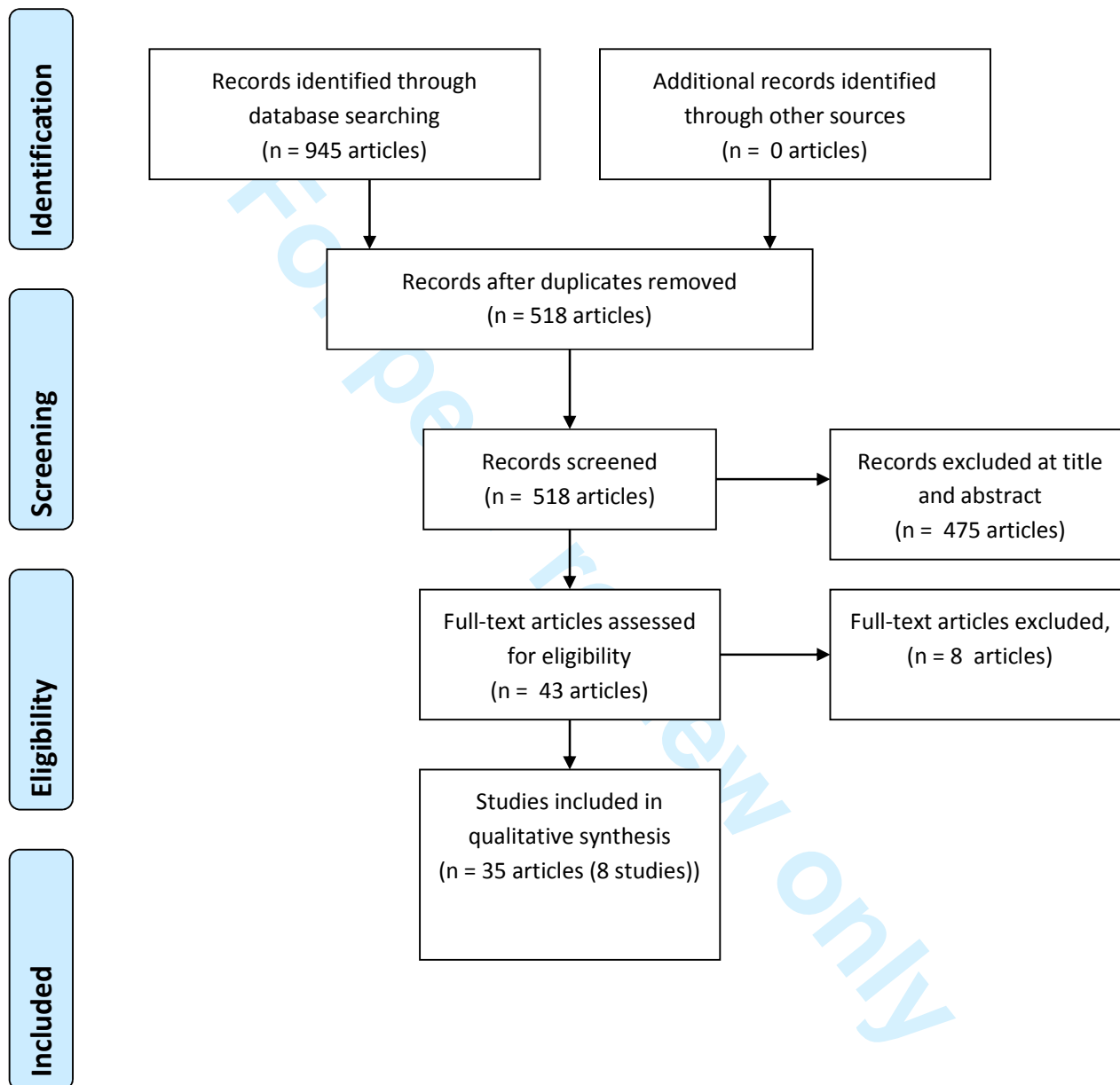
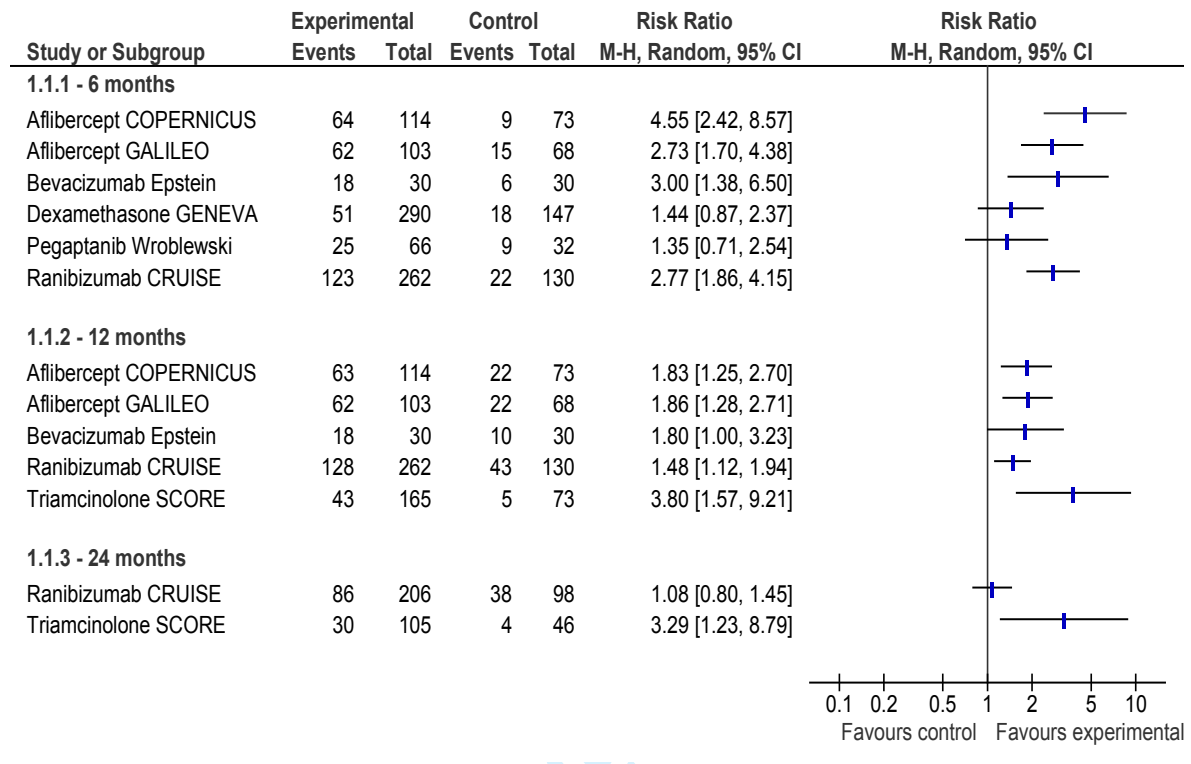


Figure 2. Study results for the primary outcome (≥ 15 ETDRS letter gain).

1 Table 1: Study characteristics

Study	Participants and baseline values	Intervention / Outcomes
DEXAMETHASONE		
<p>GENEVA 2010 ff.^{11;17;18}</p> <p>International</p> <p>Setting: multicentre (167 centres in 24 countries, so a mean of 2.6 patients per centre)</p> <p>Study aim: to evaluate the effects of dexamethasone intravitreal implant in patients with macular oedema secondary to CRVO or BRVO (only data for CRVO reported here)</p> <p>Design: 2 identical double-blind, sham-controlled RCTs, phase 3</p> <p>Follow-up: primary endpoint for the masked trial: 6 months; primary endpoint for the open-label extension: 12 months</p> <p>Overall quality: 5.5/6</p>	<p>N: CRVO – 437 eyes of 437 patients randomised; 94% follow-up at 6 months</p> <p>Inclusion criteria: ≥18 years; reduced VA due to macular oedema due to CRVO or BRVO which in the investigator’s opinion, is unlikely to be adversely affected if not treated for 6 months; duration of macular oedema 6 weeks to 9 months in patients with CRVO; BCVA 34 to 68 ETDRS letters (~20/200 and 20/50 Snellen equivalent) in the study eye and >34 letters in the non-study eye; CRT ≥300 µm (OCT)</p> <p>Exclusion criteria: <i>study eye:</i> clinically significant epiretinal membrane; use of periocular corticosteroid within 6 months or topical nonsteroidal anti-inflammatory drug or corticosteroid within 1 month; intraocular surgery or laser within 30 days of study or anticipated; history of intravitreal use of corticosteroid or any other drug; glaucoma; IOP >23 mmHg if untreated or >21 if treated with one medication; treatment with ≥2 IOP-lowering medications; active retinal, optic disc or choroidal neovascularisation; history of herpetic infection; rubeosis iridis, aphakia or anterior-chamber intraocular lens; any ocular condition that would prevent a 15-letter VA improvement; preretinal or vitreous haemorrhage, lens opacity, media opacity that would preclude clinical or photographic evaluation; history of pars plana vitrectomy; <i>any eye:</i></p>	<p>DEX 0.7 (n=136): sustained delivery, biodegradable dexamethasone intravitreal implant (Ozurdex), 0.7 mg implant inserted into the vitreous cavity through the pars plana using a customised, single-use, 22-gauge applicator</p> <p>DEX 0.35 (n=154): DEX 0.35 mg implant inserted following the same method</p> <p>Sham (n=147): a needleless applicator was placed against the conjunctiva to simulate the placement of study medication.</p> <p>Regimen for all groups: before inserting the implant, the study eye was anaesthetised with topical and subconjunctival anaesthetics and prepared according to standard clinical practice for eyes undergoing intravitreal injection; patients were treated with a topical ophthalmic antibiotic 4 times daily starting 3 days before the day of their study procedure (day 0) and continuing for 3 days after the procedure</p> <p>Extension: patients completing 180 days were eligible to enter a 6 month open label extension where they received DEX 0.7 mg implant</p> <p>Primary end point: gain of ≥15 ETDRS letters; for the open-label extension: safety</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Participants and baseline values	Intervention / Outcomes
	<p>active ocular infection; history of steroid-induced IOP–increase; diabetic retinopathy; <i>other</i>: uncontrolled systemic disease; current or anticipated use of systemic steroids or anticoagulants</p> <p>Age (years): 62.7 to 65.2 years</p> <p>Sex: 43.7 to 49.2% (CRVO and BRVO together)</p> <p>Baseline VA (ETDRS letters):52.4 SD10.6</p> <p>Baseline CRT (µm):DEX 0.7: 648; Sham: 620</p> <p>Other ocular information: phakic status (%): 85 to 88%</p> <p>Duration of macular oedema: mean 4.8 to 4.9 months;<90 days: 14.3 to 15.4%; >90 to <180 days: 54.4 to 57.4%, >180 days: 27.1 to 31.3%</p> <p>Comorbidities: diabetes mellitus 14 to 15%, hypertension 62 to 64%, coronary artery disease 9 to 13%, IOP-lowering medication at baseline 4 to 6% (all for CRVO and BRVO together)</p>	<p>Other outcomes: proportion of eyes achieving at least a 10 and 15 letter improvement from baseline; the proportion of eye exhibiting ≥15 letters of worsening; BCVA; subgroup analysis according to RVO diagnosis (BRVO and CRVO) and duration of macular oedema at baseline; CRT and safety</p> <p>Outcome assessment: evaluation at 1, 7, 30, 60, 90 and 180 days after study treatment for both parts of the study</p>
TRIAMCINOLONE		
<p>SCORE 2009 ff.¹⁹⁻³²</p> <p>USA</p> <p>Setting: multicentre</p> <p>Study aim: to compare the effects of 1 and 4 mg preservative-free</p>	<p>N: 271 eyes of 271 patients randomised; 83% (observation) and 90% (intervention) completed 12 months</p> <p>Inclusion criteria: centre-involved macular oedema secondary to CRVO, BCVA 19 to 73 ETDRS letters (Snellen equivalent ~20/400 to 20/40), CRT >250 µm by OCT; media clarity, papillary dilatation and participant</p>	<p>Tria (1 mg) (n=92): 1 mg (0.05 ml) of preservative-free, nondispersive formulation of triamcinolone (average number of injections 2.2 at 12 months)</p> <p>Tria (4 mg) (n=91): 4 mg (0.05 ml) of preservative-free, nondispersive formulation of triamcinolone(average number of injections 2.0 at 12 months)</p>

Study	Participants and baseline values	Intervention / Outcomes
<p>intravitreal triamcinolone with observation in eyes with vision loss associated with macular oedema secondary to perfused CRVO</p> <p>Design: RCT</p> <p>Follow-up: primary end point 12 months, FU planned up to 36 months</p> <p>Overall quality: 3/6</p>	<p>cooperation sufficient for adequate fundus photographs</p> <p>Exclusion criteria: macular oedema due to causes other than CRVO, ocular condition such that visual acuity would not improve from resolution of oedema, substantial cataract, prior treatment with intravitreal corticosteroids or peribulbar steroid injection within 6 months, photocoagulation (prior 4 months or anticipated), prior pars plana vitrectomy, major ocular surgery (prior 6 months or anticipated), IOP \geq25 mmHg, open-angle glaucoma, steroid-induced IOP-elevation requiring IOP-lowering treatment, pseudoexfoliation, aphakia</p> <p>Age: 68.0 SD 12.4 years</p> <p>Sex: 45% female</p> <p>Duration of macular oedema: 4.3 SD3.7 months</p> <p>Baseline VA (ETDRS letters): 51.2 SD14.1</p> <p>Baseline CRT (μm): 659 SD229</p> <p>Other ocular information: 81% phakic, IOP 15.5 SD3.2 mmHg</p> <p>Comorbidities: 23% diabetes mellitus, 73% hypertension, 21% coronary artery disease, 21% history of cancer</p>	<p>The form of triamcinolone used was Trivaris, no longer available. It was made by the manufacturer of Ozurdex (Allergan)</p> <p>Obs (n=88): observation</p> <p>Regimen for all groups: all intervention eyes received standardised ocular surface preparation prior to injection (eyelid speculum, topical anaesthetic, topical antibiotics, asepsis with povidone iodine); retreatment every 4 months unless (1) treatment was deemed successful (defined), (2) treatment was contraindicated because of significant adverse effect, (3) additional treatment was considered 'apparently futile' (defined)</p> <p>Primary end point: gain of \geq15 ETDRS letters</p> <p>Other outcomes: BCVA, intraocular pressure, eye examination including dilated fundus examination, OCT scan for thickness, , lens opacities, , adverse events</p> <p>Outcome assessment: follow-up visits every 4 months for 36 months</p>
<p>ROVO 2013³³</p>	<p>N: 90 patients randomised; 82% evaluated</p> <p>Inclusion criteria: history of CRVO not longer than 12</p>	<p>Tria (n=25): single intravitreal injection of 4 mg triamcinolone acetonide (100 μl) applied after povidone</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Participants and baseline values	Intervention / Outcomes
<p>Austria</p> <p>Setting: multicentre (7 centres in 7 countries)</p> <p>Study aim: to compare the effects of radial optical neurotomy with intravenous triamcinolone and natural history (placebo) in patients with CRVO</p> <p>Design: RCT, placebo-controlled</p> <p>Follow-up: primary end point 12 months</p> <p>Overall quality: 3.5/6</p>	<p>months; VA of ≥ 0.3 logMAR (≤ 85 letters) (for perfused CRVO: VA > 1 logMAR (> 50 letters) or no VA improvement over 4 weeks)</p> <p>Exclusion criteria: dense cataract, severe ophthalmologic conditions (severe retinopathy, presence of advanced optic atrophy, uncontrolled glaucoma), pregnancy, allergy against fluoresceine or indocyanine green, any handicap which could prevent patients from attending follow-up visits</p> <p>Age: not reported</p> <p>Sex: 36% female</p> <p>Duration of macular oedema: not reported</p> <p>Baseline VA (ETDRS letters) : 1.07 logMAR (interquartile range 0.78 to 1.7) (~46 letters)</p> <p>Baseline CRT (μm): 569 to 657 μm</p> <p>Other ocular information: not reported</p> <p>Comorbidities: 23% diabetes mellitus, 49% hypertension, 17% cardiovascular disease, 4% hypercoagulopathies, 1% leukaemia, 2% anaemia</p>	<p>iodine drops; postoperative topical antibiotics</p> <p>RON (n=38):radial optical neurotomy under general anaesthesia (detailed procedure described)</p> <p>Pla (n=20): eyes prepared as for triamcinolone injection but sham injection performed (empty syringe without needle pressed against the eye)</p> <p>Primary end point: gain of ≥ 15 ETDRS letters</p> <p>Other outcomes: BCVA, CRT, safety</p> <p>Outcome assessment: 12 months</p>
AFLIBERCEPT		
<p>COPERNICUS 2012^{34;35}</p> <p>International</p>	<p>N: 189 eyes of 189 patients randomised; 95.7% (aflibercept) and 81.1% (sham) completed 24 weeks; 93% (aflibercept) and 77% (sham) completed 52 weeks</p>	<p>VTE (n=114): intravitreal injections of 2 mg aflibercept (50 μl) every 4 weeks for 24 weeks</p> <p>Sham (n=73): sham procedure (empty syringe without</p>

Study	Participants and baseline values	Intervention / Outcomes
<p>Setting: multicentre, 70 sites in North and South America, India and Israel. Mean 2.7 patients per centre.</p> <p>Study aim: to evaluate the effects of intravitreal aflibercept in patients with macular oedema secondary to CRVO</p> <p>Design: double-blind, sham-controlled RCT, phase 3</p> <p>Follow-up: primary end point 24 weeks, FU 2 years</p> <p>Overall quality: 5/6</p>	<p>Inclusion criteria: adult patients with centre-involved CRVO for a maximum of 9 months, CRT ≥ 250 μm with OCT, ETDRS BCVA of 73 to 24 letters (Snellen equivalent 20/40 to 20/320)</p> <p>Exclusion criteria: history of vitreoretinal surgery (incl. radial optic neurotomy or sheathotomy); current bilateral retinal vein occlusion; previous pan-retinal or macular laser photocoagulation; other reasons for decreased visual acuity; ocular conditions with poorer prognosis in the fellow eye; history or presence of age-related macular degeneration, diabetic macular oedema, or diabetic retinopathy; any use of intraocular or periocular corticosteroids or antiangiogenic treatment in the study eye at any time or in the fellow eye in the preceding 3 months; iris neovascularisation, vitreous haemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula; vitreomacular traction or epiretinal membrane significantly affecting central vision; ocular inflammation; uveitis; any intraocular surgery in the preceding 3 months; aphakia; uncontrolled glaucoma, hypertension, or diabetes; spherical equivalent of a refractive error of more than -8 diopters; myopia; infectious blepharitis, keratitis, scleritis, or conjunctivitis; cerebral vascular accident or myocardial infarction in the preceding 6 months; and other conditions that could interfere with interpretation of the results or increase the risk of complications; cataract surgery was not allowed during the 3 months before randomisation.</p>	<p>needle pressed to conjunctival surface) every 4 weeks for 24 weeks</p> <p>Regimen for all groups: all patients eligible to receive pan-retinal photocoagulation for neovascularisation at any time at the discretion of the investigator; patients were not allowed to use other systemic or local medications for treating CRVO in the study eye over the first 52 weeks of the study; a noninvestigational therapy could be used to treat CRVO in the fellow eye</p> <p>Extension: during weeks 24 to 52, patients in both groups were evaluated monthly and received aflibercept if they met protocol-specified retreatment criteria, and received a sham injection if retreatment was not indicated (3.9 SE0.3 injections in the sham group and 2.7 SE0.2 injections in the VTE group); after the first year, patients continued in a 1 year extension phase with as needed dosing</p> <p>Primary end point: gain of ≥ 15 ETDRS letters</p> <p>Other outcomes: BCVA, CRT, proportion of patients progressing to neovascularisation of the anterior segment, optic disc or elsewhere in the retina, changes in vision-related quality of life (National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), safety</p> <p>Outcome assessment: examination every 4 weeks up to 24 weeks, 52 weeks</p>

Study	Participants and baseline values	Intervention / Outcomes
	<p>Age: 66.3 SD 13.9 years</p> <p>Sex: 43% female</p> <p>Time since CRVO diagnosis: 2.4 SD2.8 months; 62.0% ≤2 months, 37.4% >2 months</p> <p>Baseline VA (ETDRS letters) : 50.0 SD14.1 ; 75.4% >20/200</p> <p>Baseline CRT (µm): 665.8 SD239.8</p> <p>Other ocular information: 67.9% perfused retinal occlusion, IOP 15.1 SD3.08 mmHg</p> <p>Comorbidities: not reported</p>	
<p>GALILEO 2012^{36,37}</p> <p>International</p> <p>Setting: multicentre, 10 countries in Europe and Asia; 63 centres in total</p> <p>Study aim: to evaluate the effects of intravitreal aflibercept in patients with macular oedema secondary to CRVO</p> <p>Design: double-blind, sham-controlled RCT, phase 3</p> <p>Follow-up: primary end point 24 weeks, FU up to 12 months, planned</p>	<p>N: 177 eyes of 177 patients randomised; 90.6% (aflibercept) and 78.9% (sham) completed 24 weeks</p> <p>Inclusion criteria: treatment-naïve patients, age ≥18 years, centre-involved CRVO for a maximum of 9 months, CRT ≥250 µm with OCT, ETDRS BCVA of 73 to 24 letters (Snellen equivalent 20/40 to 20/320)</p> <p>Exclusion criteria: uncontrolled glaucoma (IOP≥25 mmHg), filtration surgery, bilateral manifestation of retinal vein occlusion, iris neovascularisation, previous treatment with anti-VEGF agents, pan-retinal or macular laser photocoagulation, intraocular corticosteroids, pregnant</p> <p>Age: 61.5 SD 12.9 years</p>	<p>VTE (n=103): intravitreal injections of 2 mg aflibercept every 4 weeks for 24 weeks</p> <p>Sham (n=71): sham procedure (empty syringe without needle pressed to conjunctival surface) every 4 weeks for 24 weeks</p> <p>Regimen for all groups: pan-retinal photocoagulation allowed at any time for all patients if they progressed to neovascularisation of the anterior segment, optic disc or fundus</p> <p>Extension: during weeks 24 to 52, patients remained in their original treatment groups but received their allocated treatment as needed; beginning from week 52 to week 76 both groups received treatment every 8</p>

Study	Participants and baseline values	Intervention / Outcomes
<p>up to 76 weeks</p> <p>Overall quality: 4/6</p>	<p>Sex: 44.4% female</p> <p>Time since CRVO diagnosis: 81.8 SD85.4 days; 52.6% <2 months, 46.2% ≥2 months, 1.2% missing</p> <p>Baseline VA (ETDRS letters) : 52.2 SD15.7, 83% >20/200</p> <p>Baseline CRT (µm): 665.5 SD231.0</p> <p>Other ocular information: 83.6% perfused retinal occlusion, IOP 14.9 SD2.7 mmHg</p> <p>Comorbidities: Renal impairment: 31% mild, 8.2% moderate, 1.2% severe; 2.9% hepatic impairment</p>	<p>weeks</p> <p>Primary end point: gain of ≥15 ETDRS letters</p> <p>Other outcomes: BCVA, CRT, proportion of patients progressing to neovascularisation of the anterior segment, optic disc or elsewhere in the fundus, changes in vision-related and overall quality of life (National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), European Quality of Life-5 Dimensions (EQ-5D)), safety</p> <p>Outcome assessment: 24 weeks, 52 weeks</p>
PEGAPTANIB		
<p>Wroblewski 2009³⁸⁻⁴⁴</p> <p>International</p> <p>Number of sites: not reported</p> <p>Setting: multicentre, practitioners' offices and clinics in Australia, France, Germany, Israel, Spain, USA</p> <p>Study aim: to evaluate the effects of intravitreal pegaptanib sodium in patients with macular oedema secondary to CRVO</p> <p>Design: double-blind, sham-</p>	<p>N: 98 eyes of 98 patients randomised; 93% completed 30 weeks</p> <p>Inclusion criteria: age ≥18 years, CRVO with onset within 6 months prior to baseline, CRT ≥250 µm with OCT, ETDRS BCVA of 65 to 20 letters (Snellen equivalent 20/50 to 20/400) and better than 35 letters (20/200) in the fellow eye</p> <p>Exclusion criteria: subtenon corticosteroid administration for any ophthalmic condition; prior panretinal or sector scatter photocoagulation; signs of old branch retinal vein occlusion or CRVO in the study eye; any other retinal vascular disease including diabetic retinopathy; eyes with a brisk afferent pupillary defect;</p>	<p>PS 0.3 mg (n=33): intravitreal injections of 0.3 mg pegaptanib sodium every 6 weeks for 24 weeks (5 injections)</p> <p>PS 1 mg (n=33): intravitreal injections of 1 mg pegaptanib sodium every 6 weeks for 24 weeks (5 injections)</p> <p>Sham (n=32): sham procedure (blunt pressure applied to the globe without a needle) every 6 weeks for 24 weeks</p> <p>Regimen for all groups: antisepsis procedures were the same for all participants (including those receiving sham); all participants received injected subconjunctival anaesthetic; panretinal photocoagulation permitted at</p>

Study	Participants and baseline values	Intervention / Outcomes
<p>controlled RCT, phase 2</p> <p>Follow-up: primary end point 30 weeks, FU up to 12 months</p> <p>Overall quality: 6/6</p>	<p>vitreous haemorrhage except for breakthrough haemorrhage from intraretinal haemorrhage; evidence of any neovascularisation involving the iris, disc, or retina; any other clinically significant concomitant ocular diseases</p> <p>Age: 59 to 64 years</p> <p>Sex: 47% female</p> <p>Time from occlusive event to study entry: 77 to 82 days</p> <p>Baseline VA (ETDRS letters): 47.6 to 48.5 letters</p> <p>Baseline CRT (μm): 632 to 688</p> <p>Other ocular information: not reported</p> <p>Comorbidities: not reported</p>	<p>any time point for neovascularisation according to the Central Vein Occlusion Study protocol; intravitreal steroids not permitted at any time</p> <p>Extension: FU to 52 weeks</p> <p>Primary end point: gain of ≥ 15 ETDRS letters</p> <p>Other outcomes: BCVA, loss of ≥ 15 letters, CRT, proportion of eyes progressing to retinal or iris neovascularisation, safety</p> <p>Outcome assessment: assessments every 6 weeks up to week 30, FU to week 52</p>
RANIBIZUMAB		
<p>CRUISE 2010 ff.^{10,45,46}</p> <p>USA</p> <p>Number of sites: not reported</p> <p>Setting: multicentre</p> <p>Study aim: to evaluate the effects of intravitreal ranibizumab (0.3 or 0.5 mg) in patients with macular oedema secondary to CRVO</p>	<p>N: 392 eyes of 392 patients randomised; 97.7% (ran 0.3 mg), 91.5% (ran 0.5 mg), and 88.5% (sham) completed 6 months</p> <p>Inclusion criteria: age ≥ 18 years, foveal centre-involved macular oedema secondary to CRVO diagnosed within 12 months before study began, CRT $\geq 250 \mu\text{m}$ with OCT, BCVA 20/40 to 20/320 (ETDRS charts)</p> <p>Exclusion criteria: prior episode of retinal vein</p>	<p>Ran 0.3 mg (n=132): intravitreal injections of 0.3 mg ranibizumab monthly for 6 months (maximum 6 injections)</p> <p>Ran 0.5 mg (n=130): intravitreal injections of 0.5 mg ranibizumab monthly for 6 months (maximum 6 injections)</p> <p>Sham (n=130): sham procedure (empty syringe without needle pressed to the injection site) monthly for 6 months</p>

Study	Participants and baseline values	Intervention / Outcomes
<p>Design: double-blind, sham-controlled RCT, phase 3</p> <p>Follow-up: primary end point 6 months, FU up to 12 months</p> <p>Overall quality: 4.5/6</p>	<p>occlusion, brisk afferent pupillary defect, >10-letter improvement in BCVA between screening and day 0, history of radial optic neurotomy or sheathotomy, intraocular corticosteroid use in study eye in prior 3 months, history or presence of wet or dry age-related macular oedema, recent or anticipated panretinal scatter photocoagulation or sector laser photocoagulation, laser photocoagulation for macular oedema in prior 4 months, evidence on examination of any diabetic retinopathy, stroke or myocardial infarction in prior 3 months, prior anti-VEGF treatment in study or fellow eye in prior 3 months or systemic anti-VEGF or pro-VEGF treatment in prior 6 months</p> <p>Age: 65.4 SD13.1 to 69.7 SD11.6 years</p> <p>Sex: 38.5 to 46.2% female</p> <p>Time since CRVO diagnosis: 2.9 SD2.9 to 3.6 SD3.2 months; 65.9 to 72.3% ≤3 months</p> <p>Baseline VA (ETDRS letters): 47.4 to 49.2 (SD 14.6 to 14.8) (range 9 to 72), 38.5 to 42.3% ≥55</p> <p>Baseline CRT (µm): 679.9 SD242.4 to 688.7 SD253.1</p> <p>Other ocular information: IOP 14.9 SD3.3 to 15.1 SD3.1 mmHg, 10.0 to 16.9% IOP-lowering medication, n=2 >10 disc areas of non-perfusion; fellow eye BCVA 78.8 SD 17.4 to 80.0 SD12.5</p>	<p>Regimen for all groups: prior to injection or sham: topical anaesthetic drops, subconjunctival injection of 2% lidocaine, cleaning of injection site with 5% povidone iodine</p> <p>Extension: months 6 to 12: all patients could receive intraocular ranibizumab (previously assigned dose or 0.5 mg for the sham group) if they met pre-specified functional and anatomic criteria (3.7 injections sham group, 3.8 injections 0.3 mg ran group, 3.3 injections 0.5 mg ran group); after 12 months' FU, 304 CRUISE patients continued in the HORIZON study for another 12 months, where patients were evaluated at least every 3 months and were eligible to receive an intravitreal injection of 0.5 mg ranibizumab if they fulfilled prespecified criteria (2.9 SD2.7 injections sham group, 3.8 SD2.8 injections 0.3 mg ran group, 3.5 SD2.7 injections 0.5 mg ran group)</p> <p>Primary end point: mean change from baseline BCVA</p> <p>Other outcomes: percentage gaining ≥15 letters, percentage losing ≥15 letters, CRT, percentage with CRT <250 µm, vision-related quality of life (National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), safety</p> <p>Outcome assessment: monthly visits up to 12 months; 3-monthly evaluation up to 24 months (HORIZON)</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Participants and baseline values	Intervention / Outcomes
	Comorbidities: not reported	
BEVACIZUMAB		
<p>Epstein 2012⁴⁷⁻⁴⁹</p> <p>Sweden</p> <p>Setting: Single centre; St. Eriks Eye Hospital Stockholm</p> <p>Study aim: to evaluate the effects of intraocular injections of bevacizumab in patients with macular oedema secondary to CRVO</p> <p>Design: sham-injection controlled, double masked RCT</p> <p>Follow-up: primary end-point 6 months; open label extension up to 12 months</p> <p>Overall quality: 5/6</p>	<p>N: 60 eyes of 60 patients randomised; 93% completed open label extension</p> <p>Inclusion criteria: CRVO of ≤6 months; BCVA 15 to 65 ETDRS letters (Snellen equivalent ~20/50 to 20/500), CRT ≥300 µm by OCT</p> <p>Exclusion criteria: CRVO with neovascularisation; previous treatment for CRVO; intraocular surgery during previous 3 months; vascular retinopathy of other causes; glaucoma with advanced visual field defect or uncontrolled ocular hypertension >25 mmHg despite full therapy; myocardial infarction or stroke during last 12 months</p> <p>Age: 70.5 SD 12.6 years</p> <p>Sex: 40% female</p> <p>Time from diagnosis to inclusion: 8.8 SD 5.7 weeks; 71.7% <90 days, 28.3% >90 days</p> <p>Baseline VA (ETDRS letters) : 44.1 SD 15.5 ; 31.7% <34, 68.3% >34</p>	<p>Bev (n=30): 1.25 mg (0.05 ml) bevacizumab via pars plana</p> <p>Sham (n=30): sham injection (syringe without needle pressed to the globe)</p> <p>Regimen for all groups: 4 injections received, one every 6 weeks; eyes treated with topical antibiotics 30 min before injection, topical chlorhexidine, topical anaesthesia with 1% tetracaine</p> <p>Open label extension: months 6 to 12, intravitreal bevacizumab injections every 6 weeks (4 injections) for all patients</p> <p>Primary end point: gain of ≥15 ETDRS letters</p> <p>Other outcomes: BCVA, OCT images, CRT, fluorescein angiogram, colour and red-free photography, slit-lamp examination with dilated fundus-examination, intraocular pressure, adverse events</p> <p>Outcome assessment: follow-up visits every 6 weeks up to 24 weeks</p>

Study	Participants and baseline values	Intervention / Outcomes
	Baseline CRT (μm): 721 SD 269 Comorbidities: 48.3% hypertension, 6.7% diabetes mellitus	

2 **Abbreviations:** BCVA – best corrected visual acuity, CRT – central retinal thickness, CRVO – central retinal vein occlusion, ETDRS – Early Treatment Diabetic
3 Retinopathy Study, FU – follow-up, IOP – intraocular pressure, OCT – optical coherence tomography, SD – standard deviation, SE – standard error

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

6 Table 2: Study results and adverse events

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events
DEXAMETHASONE		

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events					
GENEVA 2010 ff. ^{11;17;18}		Baseline	6 months	p	12 months	p	AE	DEX 0.35	DEX 0.7 (n = 133)	Sham (n = 147)	p
	BCVA (mean letters)						6 months				
	<i>DEX 0.35</i>	-	-				Overall incidence of ocular adverse events				
	<i>DEX 0.7</i>	52.4 SD 10.6	+0.1	< 0.001 vs sham	<i>DEX 0.7/0.7</i>	+2 (estimated from graph)		68.4%	49.7%		
	<i>Sham</i>	53.3 SD 10.8	-1.8		<i>Sham/DEX 0.7</i>	-1.4 (ditto)	Common Ocular Adverse Events				
	≥15 letters gained						Intraocular pressures increased	40 (30.1%)	2 (1.4%)	<0.001	
	<i>DEX 0.35</i>		17%	NS vs sham			Common treatment-related Ocular Adverse Events				
	<i>DEX 0.7</i>		18.4%	NS vs sham	<i>DEX 0.7/0.7, day 240</i>	27%	IOP increased	39 (29.3%)	1 (0.7%)	<0.001	
					<i>DEX 0.7 (n=19), day 360</i>	26%	Cataract adverse events				
	<i>Sham</i>		12.2%	NS vs sham	<i>Sham/DEX 0.7, day 240</i>	21%	Cataract	3 (2.3%)	2 (1.4%)		
	≥15 letters lost						Cataract subcapsular	4 (3.0%)	1 (0.7%)		
	<i>DEX 0.35</i>		-	-			Cataract nuclear	3 (2.3%)	1 (0.7%)		
	<i>DEX 0.7</i>		14.0%	NS			Cataract cortical	1 (0.8%)	3 (2.0%)		
	<i>Sham</i>		20.4%				Serious adverse events – not given separately for CRVO				
	Subgroups										
Duration of macular oedema											
>90 days	<i>DEX 0.7</i>	17.7%									
	<i>Sham</i>	9.6%									
≤90 days	<i>DEX 0.7</i>	26.0%									
	<i>Sham</i>	27.3%									

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events																																								
	<p>CRT (µm):</p> <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>6months (mean)</th> <th>p</th> <th>12 months (mean)</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>CRT</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>DEX 0.35</td> <td>-</td> <td>-</td> <td></td> <td></td> <td></td> </tr> <tr> <td>DEX 0.7</td> <td>647.6</td> <td>-118.2</td> <td>NS vs sham</td> <td></td> <td></td> </tr> <tr> <td>Sham</td> <td>619.8</td> <td>-125.3</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>		Baseline	6months (mean)	p	12 months (mean)	p	CRT						DEX 0.35	-	-				DEX 0.7	647.6	-118.2	NS vs sham			Sham	619.8	-125.3														
	Baseline	6months (mean)	p	12 months (mean)	p																																					
CRT																																										
DEX 0.35	-	-																																								
DEX 0.7	647.6	-118.2	NS vs sham																																							
Sham	619.8	-125.3																																								
TRIAMCINOLONE																																										
<p>SCORE 2009 ff.¹⁹⁻³²</p> <p>1 mg intravitreal triamcinolone (2.2 injections over 12 months) (n=92)</p> <p>versus 4 mg intravitreal triamcinolone (2</p>	<p>BCVA (ETDRS letters):</p> <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>12 months</th> <th>p</th> <th>24 months</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>BCVA (letters, 95% CI)</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Tria 1 mg</td> <td>50.6 SD 14.9</td> <td>-1.2 (-6.4 to +4.1)</td> <td><0.05 vs obs</td> <td>-4.4 (-11.5 to +2.8)</td> <td>NR</td> </tr> <tr> <td>Tria 4 mg</td> <td>51.0 SD 14.4</td> <td>-1.2 (-6.3 to +4.0)</td> <td><0.05 vs obs</td> <td>-2.4 (-9.3 to +4.4)</td> <td></td> </tr> </tbody> </table>		Baseline	12 months	p	24 months	p	BCVA (letters, 95% CI)						Tria 1 mg	50.6 SD 14.9	-1.2 (-6.4 to +4.1)	<0.05 vs obs	-4.4 (-11.5 to +2.8)	NR	Tria 4 mg	51.0 SD 14.4	-1.2 (-6.3 to +4.0)	<0.05 vs obs	-2.4 (-9.3 to +4.4)		<p>Ocular Adverse Events</p> <table border="1"> <thead> <tr> <th>AE</th> <th>Tria 1 mg</th> <th>Tria 4 mg</th> <th>Obs</th> </tr> </thead> <tbody> <tr> <td>12 months</td> <td></td> <td></td> <td></td> </tr> <tr> <td><i>Elevated IOP or glaucoma</i></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Initiation of IOP-lowering medication</td> <td>20%</td> <td>35%</td> <td>8%</td> </tr> </tbody> </table>	AE	Tria 1 mg	Tria 4 mg	Obs	12 months				<i>Elevated IOP or glaucoma</i>				Initiation of IOP-lowering medication	20%	35%	8%
	Baseline	12 months	p	24 months	p																																					
BCVA (letters, 95% CI)																																										
Tria 1 mg	50.6 SD 14.9	-1.2 (-6.4 to +4.1)	<0.05 vs obs	-4.4 (-11.5 to +2.8)	NR																																					
Tria 4 mg	51.0 SD 14.4	-1.2 (-6.3 to +4.0)	<0.05 vs obs	-2.4 (-9.3 to +4.4)																																						
AE	Tria 1 mg	Tria 4 mg	Obs																																							
12 months																																										
<i>Elevated IOP or glaucoma</i>																																										
Initiation of IOP-lowering medication	20%	35%	8%																																							

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events				
injections over 12 months (n=91) versus observation (n=88)	Obs	52.1 SD 13.1	-12.1 (-17.1 to -7.1)		-10.7 (-17.4 to -4.1)	IOP >35 mm Hg (n)	5	8	1	
	≥15 letters gained (95% CI)					IOP >10 mm Hg above baseline (n)	15	24	2	
	Tria 1 mg		26.5% (17 to 36)	0.001 vs obs	31% (19 to 43)	NR	Laser peripheral iridotomy (n)	0	1	0
	Tria 4 mg		25.6% (16 to 35)	0.001 vs obs	26% (14 to 38)		Trabeculectomy (n)	0	0	0
	Obs		6.8% (1 to 13)		9% (1 to 17)		Tube shunt (n)	2	0	0
	≥15 letters lost						<i>Cataract</i>			
	Tria 1 mg		25.3%		31%		Lens opacity onset or progression	26%	33%	18%
	Tria 4 mg		25.6%		26%		Cataract surgery (n)	0	4	0
	Obs		43.8%		48%	NS, p=0.06 tria vs obs	<i>At least 1 of the following adverse events (n):</i>	11	6	9
	CRT (µm):						Infectious endophthalmitis (n)	0	0	0
		Baseline	12 months (median, IQR)	p	24 months (median, IQR)	p	Non-infectious endophthalmitis (n)	0	0	0

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events			
	CRT						Retinal detachment (n)	0	0	0
	Triia 1 mg	643 SD 226	-196 (-390 to -62)	NR	-286 (-458 to -119)	NR	Iris neovascularisation or neovascular glaucoma	9	4	2
	Triia 4 mg	641 SD 248	-261 (-407 to -79)		-236 (-421 to -63)		Retinal neovascularisation (n)	2	2	4
	Obs	695 SD 208	-277 (-418 to -40)		-304 (-465 to -108)		Vitreous hemorrhage (n)	4	0	4
	CRT <250 µm			CRT <250 µm			<i>Other ocular surgical procedures</i>			
	Triia 1 mg		32%	NR	50%	NR	YAG capsulotomy	0	0	1
	Triia 4 mg		45%		39%		Sector or panretinal scatter photocoagulation	9	3	5
	Obs		28%		38%		Pars plana vitrectomy	2	0	1
	Results for subgroups (based on baseline BCVA (73 to 59, 58 to 49, 48 to 19), baseline CRT (<500 µm, ≥500 µm), duration of macular oedema (≤3 months, >3 months, pseudophakic at baseline) were consistent with the overall results (significance levels for comparisons not reported))						Selected Events at 12-24 months			
							<i>Glaucoma procedures</i>			
							Laser peripheral iridotomy	0	0	0

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events																																																																				
		<table border="1"> <tr> <td>Trabeculectomy</td> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td>Tube shunt</td> <td>0</td> <td>2</td> <td>0</td> </tr> <tr> <td colspan="4"><i>Cataract</i></td> </tr> <tr> <td>Cataract surgery</td> <td>3</td> <td>21</td> <td>0</td> </tr> <tr> <td colspan="4">Reports of systemic adverse events were similar between groups</td> </tr> </table>	Trabeculectomy	0	0	0	Tube shunt	0	2	0	<i>Cataract</i>				Cataract surgery	3	21	0	Reports of systemic adverse events were similar between groups																																																			
Trabeculectomy	0	0	0																																																																			
Tube shunt	0	2	0																																																																			
<i>Cataract</i>																																																																						
Cataract surgery	3	21	0																																																																			
Reports of systemic adverse events were similar between groups																																																																						
ROVO 2013³³ 4 mg intravitreal triamcinolone acetonide (single injection) versus radial optical neurotomy versus sham injection	BCVA (logMAR): <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>12 months</th> <th>p</th> </tr> </thead> <tbody> <tr> <td colspan="4">BCVA (logMAR, interquartile range)</td> </tr> <tr> <td><i>Tria 4 mg</i></td> <td>1.02 (0.75, 2.0)</td> <td>0.86 (0.51, 1.78) (-0.16)</td> <td>NR</td> </tr> <tr> <td><i>RON</i></td> <td>1.46 (0.84, 2.0)</td> <td>0.75 (46, 1.22) (-0.71)</td> <td></td> </tr> <tr> <td><i>Sham</i></td> <td>1.02 (0.9, 1.36)</td> <td>1.02 (0.85, 3.0) (0)</td> <td></td> </tr> <tr> <td colspan="4">% with VA improvement</td> </tr> <tr> <td><i>Tria 4 mg</i></td> <td></td> <td>20%</td> <td>0.034 vs RON, NS vs placebo</td> </tr> <tr> <td><i>RON</i></td> <td></td> <td>47%</td> <td></td> </tr> </tbody> </table>		Baseline	12 months	p	BCVA (logMAR, interquartile range)				<i>Tria 4 mg</i>	1.02 (0.75, 2.0)	0.86 (0.51, 1.78) (-0.16)	NR	<i>RON</i>	1.46 (0.84, 2.0)	0.75 (46, 1.22) (-0.71)		<i>Sham</i>	1.02 (0.9, 1.36)	1.02 (0.85, 3.0) (0)		% with VA improvement				<i>Tria 4 mg</i>		20%	0.034 vs RON, NS vs placebo	<i>RON</i>		47%		Ocular Adverse Events, 12 months <table border="1"> <thead> <tr> <th>AE</th> <th><i>Tria 4 mg</i></th> <th><i>RON</i></th> <th><i>Pla</i></th> </tr> </thead> <tbody> <tr> <td>Retinal detachment</td> <td></td> <td>7.9%</td> <td></td> </tr> <tr> <td>Subretinal haemorrhages</td> <td></td> <td>5.3%</td> <td></td> </tr> <tr> <td>Vitreous haemorrhage</td> <td></td> <td>2.6%</td> <td>10%</td> </tr> <tr> <td>Subretinal membrane formation</td> <td></td> <td>2.6%</td> <td></td> </tr> <tr> <td>Retinal tear</td> <td></td> <td>2.6%</td> <td></td> </tr> <tr> <td>IOP increase</td> <td>32%</td> <td></td> <td></td> </tr> <tr> <td>Cataract progression</td> <td>24%</td> <td>13%</td> <td>15%</td> </tr> <tr> <td>Neovascular glaucoma</td> <td>12%</td> <td>5%</td> <td>15%</td> </tr> </tbody> </table>	AE	<i>Tria 4 mg</i>	<i>RON</i>	<i>Pla</i>	Retinal detachment		7.9%		Subretinal haemorrhages		5.3%		Vitreous haemorrhage		2.6%	10%	Subretinal membrane formation		2.6%		Retinal tear		2.6%		IOP increase	32%			Cataract progression	24%	13%	15%	Neovascular glaucoma	12%	5%	15%
	Baseline	12 months	p																																																																			
BCVA (logMAR, interquartile range)																																																																						
<i>Tria 4 mg</i>	1.02 (0.75, 2.0)	0.86 (0.51, 1.78) (-0.16)	NR																																																																			
<i>RON</i>	1.46 (0.84, 2.0)	0.75 (46, 1.22) (-0.71)																																																																				
<i>Sham</i>	1.02 (0.9, 1.36)	1.02 (0.85, 3.0) (0)																																																																				
% with VA improvement																																																																						
<i>Tria 4 mg</i>		20%	0.034 vs RON, NS vs placebo																																																																			
<i>RON</i>		47%																																																																				
AE	<i>Tria 4 mg</i>	<i>RON</i>	<i>Pla</i>																																																																			
Retinal detachment		7.9%																																																																				
Subretinal haemorrhages		5.3%																																																																				
Vitreous haemorrhage		2.6%	10%																																																																			
Subretinal membrane formation		2.6%																																																																				
Retinal tear		2.6%																																																																				
IOP increase	32%																																																																					
Cataract progression	24%	13%	15%																																																																			
Neovascular glaucoma	12%	5%	15%																																																																			

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				Adverse events				
	<i>Sham</i>	10%		0.009 vs RON	Rubeosis iridis 15%				
	% with VA deterioration				No cases of phthisis, enucleation, endophthalmitis, injury of central vessels, injury of optic nerve				
	<i>Tria 4 mg</i>	NR							
	<i>RON</i>	8%							
	<i>Sham</i>	35%		0.007 vs RON					
	CRT (µm):								
			Baseline	12 months	p				
	CRT								
	<i>Tria 4 mg</i>	657	-235	NS					
	<i>RON</i>	569	-263	NS					
<i>Sham</i>	615	-206							
AFLIBERCEPT									
COPERNICUS 2012 ^{34;35} 2 mg intravitreal aflibercept (every 4 weeks over 24	BCVA (ETDRS letters):				Adverse Events				
			Baseline	24 weeks	p	52 weeks (all VTE PRN)	AE (24 weeks)	VTE	Sham
	BCVA (letters)				Discontinued treatment before week 24 because of AE	0	4.1%		
					At least one AE	83.3%	85.1%		

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events			
weeks)(n=114) versus sham injection (n=73)	VTE	50.7 SD 13.9	+17.3	<0.001	+16.2	<0.001	Ocular AEs	68.4%	68.9%	
	Sham	48.9 SD 14.4	-4.0		+3.8		Patients with at least one serious adverse event	3.5%	13.5%	
extension up to 52 weeks with afibercept PRN in both groups	≥15 letters gained						Vitreous haemorrhage	0	5.4%	
	VTE		56.1%	<0.001	55.3%	<0.001	Neovascular glaucoma	0	2.7%	
	Sham		12.3%		30.1%		Iris neovascularisation	0	2.7%	
	≥10 letters lost						Retinal haemorrhage	0	2.7%	
	VTE		1.8%	NR			Visual acuity reduced	0.9%	1.4%	
	Sham		30.1%				Retinal artery occlusion	0.9%	0	
	Subgroups						Retinal tear	0	1.4%	
	Baseline VA		≥15 letters gained				Retinal vein occlusion	0	1.4%	
	VTE ≤20/200	VTE		67.9%	NR	60.7%	NR	Endophthalmitis	0.9%	0
		Sham		16.7%		22.2%		Corneal abrasion	0.9%	0
VTE >20/200	VTE		52.3%		53.5%		AE (24 to 52 weeks)	VTE	Sham	
	Sham		10.9%		32.7%		Patients with at least one serious adverse event	2.7%	3.3%	
Time since diagnosis						Vitreous haemorrhage	0.9%	1.7%		
VTE <2 mo	VTE		68.8%	NR	64.1%	NR	Glaucoma	0	1.7%	

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events				
	<i>Sham</i>		15.4%			34.6%			Iris neovascularisation	0	0
	VTE ≥2 mo	<i>VTE</i>	38.8%			42.9%			Retinal haemorrhage	0	0
		<i>Sham</i>	4.8%			19.0%			Visual acuity reduced	0	0
	Perfusion status								Retinal artery occlusion	0	0
	VTE perfused	<i>VTE</i>	58.4%	NS		58.4%	NR		Retinal tear	0	1.7%
		<i>Sham</i>	16%			30.0%			Retinal vein occlusion	0.9%	0
	VTE non-perfused	<i>VTE</i>	51.4%			48.6%			Cataract	0.9%	0
		<i>Sham</i>	4.3%			30.4%			Cystoid macular oedema	0.9%	0
	CRT (µm):								Endophthalmitis	0	0
		Baseline	24 weeks	p		52 weeks (all VTE PRN)	p		Corneal abrasion	0	0
	CRT								Reports of systemic adverse events were similar between groups; 2 deaths in the sham group by 24 weeks; 2.7% arterial thromboembolic events in the sham group and 0.9% in the intervention group		
	<i>VTE</i>	661.7 SD 237.4	-457.2	<0.001		-413.0	NS				
	<i>Sham</i>	672.4 SD 245.3	-144.8			-381.8					
	QoL										
		Baseline	24 weeks	p		52 weeks (all VTE PRN)	p				

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events
	PRN)						
	NEI-VFQ-25 total						
	VTE	77.76 SD 15.96	+7.2 SD 12.1	0.001	+7.5	NS	
	Sham	77.78 SD 16.25	+0.8 SD 9.8		+5.1		
	NEI-VFQ-25 near activities						
	VTE	69.96 SD 21.94	+8.3 SD 22.0	<0.05	+11.4	NS	
	Sham	70.72 SD 20.22	+1.84 SD 19.75		+8.3		
	NEI-VFQ-25 distance activities						
	VTE	75.99 SD 21.26	+6.1 SD 20.0	<0.05	+8.5	NS	
	Sham	78.08 SD 21.25	-0.64 SD 15.2		+3.8		
	NEI-VFQ-25 vision dependency						
	VTE	83.26 SD 25.51	+7.1 SD 20.5	<0.05	+6.0	NS	
	Sham	82.76 SD 27.41	+1.1 SD 20.5		+3.4		

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events																																																																																																																								
	Progression to neovascularisation: 0 with aflibercept, 6.8% with sham treatment over 52 weeks, p=0.006 Perfused status at week 24: 78.9% with aflibercept, 46.6% with sham treatment																																																																																																																									
GALILEO 2012^{36;37} 2 mg intravitreal aflibercept (every 4 weeks over 24 weeks) (n=103) versus sham injection (n=71) extension up to 52 weeks	BCVA (ETDRS letters): <table border="1" data-bbox="380 495 1438 1367"> <thead> <tr> <th></th> <th>Baseline</th> <th>24 weeks</th> <th>p</th> <th>52 weeks</th> <th>p</th> </tr> </thead> <tbody> <tr> <td colspan="6">BCVA (letters)</td> </tr> <tr> <td>VTE</td> <td>53.6 SD15.8</td> <td>+18.0</td> <td><0.0001</td> <td>+16.9</td> <td><0.0001</td> </tr> <tr> <td>Sham</td> <td>50.9 SD15.4</td> <td>+3.3</td> <td></td> <td>+3.8</td> <td></td> </tr> <tr> <td colspan="6">≥15 letters gained</td> </tr> <tr> <td>VTE</td> <td></td> <td>60.2%</td> <td><0.0001</td> <td>60.2%</td> <td>0.0004</td> </tr> <tr> <td>Sham</td> <td></td> <td>22.1%</td> <td></td> <td>32.4%</td> <td></td> </tr> <tr> <td colspan="6">≥10 letters lost</td> </tr> <tr> <td>VTE</td> <td></td> <td>7.8%</td> <td>0.0033</td> <td></td> <td></td> </tr> <tr> <td>Sham</td> <td></td> <td>25.0%</td> <td></td> <td></td> <td></td> </tr> <tr> <td colspan="6">Subgroups</td> </tr> <tr> <td colspan="2">Time since diagnosis</td> <td colspan="4">≥15 letters gained</td> </tr> <tr> <td>VTE <2 mo</td> <td></td> <td>70.9%</td> <td>NR</td> <td></td> <td></td> </tr> </tbody> </table>		Baseline	24 weeks	p	52 weeks	p	BCVA (letters)						VTE	53.6 SD15.8	+18.0	<0.0001	+16.9	<0.0001	Sham	50.9 SD15.4	+3.3		+3.8		≥15 letters gained						VTE		60.2%	<0.0001	60.2%	0.0004	Sham		22.1%		32.4%		≥10 letters lost						VTE		7.8%	0.0033			Sham		25.0%				Subgroups						Time since diagnosis		≥15 letters gained				VTE <2 mo		70.9%	NR			Ocular Adverse Events <table border="1" data-bbox="1486 495 2074 1367"> <thead> <tr> <th>AE</th> <th>VTE</th> <th>Sham</th> </tr> </thead> <tbody> <tr> <td>Discontinued treatment before week 24 because of AE</td> <td>1.9%</td> <td>11.3%</td> </tr> <tr> <td>Eye pain</td> <td>11.5%</td> <td>4.4%</td> </tr> <tr> <td>Conjunctival haemorrhage</td> <td>8.7%</td> <td>4.4%</td> </tr> <tr> <td>Retinal exudates</td> <td>6.7%</td> <td>7.4%</td> </tr> <tr> <td>Foreign body sensation</td> <td>5.8%</td> <td>7.4%</td> </tr> <tr> <td>Retinal vascular disorder</td> <td>5.8%</td> <td>8.8%</td> </tr> <tr> <td>Ocular hyperaemia</td> <td>4.8%</td> <td>5.9%</td> </tr> <tr> <td>Vitreous floaters</td> <td>4.8%</td> <td>0</td> </tr> <tr> <td>Macular oedema</td> <td>3.8%</td> <td>16.2%</td> </tr> <tr> <td>Macular ischaemia</td> <td>3.8%</td> <td>4.4%</td> </tr> <tr> <td>Optic disc vascular disorder</td> <td>3.8%</td> <td>4.4%</td> </tr> <tr> <td>Eye irritation</td> <td>2.9%</td> <td>10.3%</td> </tr> <tr> <td>Lacrimation increased</td> <td>2.9%</td> <td>5.9%</td> </tr> </tbody> </table>	AE	VTE	Sham	Discontinued treatment before week 24 because of AE	1.9%	11.3%	Eye pain	11.5%	4.4%	Conjunctival haemorrhage	8.7%	4.4%	Retinal exudates	6.7%	7.4%	Foreign body sensation	5.8%	7.4%	Retinal vascular disorder	5.8%	8.8%	Ocular hyperaemia	4.8%	5.9%	Vitreous floaters	4.8%	0	Macular oedema	3.8%	16.2%	Macular ischaemia	3.8%	4.4%	Optic disc vascular disorder	3.8%	4.4%	Eye irritation	2.9%	10.3%	Lacrimation increased	2.9%	5.9%
	Baseline	24 weeks	p	52 weeks	p																																																																																																																					
BCVA (letters)																																																																																																																										
VTE	53.6 SD15.8	+18.0	<0.0001	+16.9	<0.0001																																																																																																																					
Sham	50.9 SD15.4	+3.3		+3.8																																																																																																																						
≥15 letters gained																																																																																																																										
VTE		60.2%	<0.0001	60.2%	0.0004																																																																																																																					
Sham		22.1%		32.4%																																																																																																																						
≥10 letters lost																																																																																																																										
VTE		7.8%	0.0033																																																																																																																							
Sham		25.0%																																																																																																																								
Subgroups																																																																																																																										
Time since diagnosis		≥15 letters gained																																																																																																																								
VTE <2 mo		70.9%	NR																																																																																																																							
AE	VTE	Sham																																																																																																																								
Discontinued treatment before week 24 because of AE	1.9%	11.3%																																																																																																																								
Eye pain	11.5%	4.4%																																																																																																																								
Conjunctival haemorrhage	8.7%	4.4%																																																																																																																								
Retinal exudates	6.7%	7.4%																																																																																																																								
Foreign body sensation	5.8%	7.4%																																																																																																																								
Retinal vascular disorder	5.8%	8.8%																																																																																																																								
Ocular hyperaemia	4.8%	5.9%																																																																																																																								
Vitreous floaters	4.8%	0																																																																																																																								
Macular oedema	3.8%	16.2%																																																																																																																								
Macular ischaemia	3.8%	4.4%																																																																																																																								
Optic disc vascular disorder	3.8%	4.4%																																																																																																																								
Eye irritation	2.9%	10.3%																																																																																																																								
Lacrimation increased	2.9%	5.9%																																																																																																																								

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)						Adverse events		
	VTE ≥2 mo		50.0%				Papilloedema	1.9%	4.4%
							Retinal ischaemia	1.0%	4.4%
	CRT (µm):						Visual acuity reduced	0	10.3%
	Baseline	24 weeks	p	52 weeks	p	IOP increased	9.6%	5.9%	
	CRT						Injection site pain	4.8%	2.9%
	VTE	683.2 SD234.5	-448.6	<0.0001	-423.5	<0.0001	Serious adverse events		
	Sham	638.7 SD224.7	-169.3		-219.3		At least 1 SAE	1.9% 5.9%	
	QoL						Glaucoma	0	2.9%
	Baseline	24 weeks	p	52 weeks	p	Macular oedema	1.0%	1.5%	
	NEI-VFQ						Retinal tear	1.0%	0
	VTE		+7.5	0.0013			Vitreous detachment	1.0% 0	
	Sham		+3.5				Reports of systemic adverse events were similar between groups; no arterial thromboembolic events or deaths during 24 weeks		
	Percentage of any patients progressing to any neovascularisation by week 24, difference between groups -1.5 (95% CI: -7.4 to 4.4)						No endophthalmitis or cases of rhegmatogenous detachment, one incidence of uveitis in VTE group considered mild and resolved without change in therapy		
	No significant differences on the EQ-5D score between groups								

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events																																																																														
PEGAPTANIB																																																																																
Wroblewski 2009³⁸⁻⁴⁴ 0.3 mg intravitreal pegaptanib sodium (every 6 weeks over 24 weeks) (n=33) versus 1 mg intravitreal pegaptanib sodium (every 6 weeks over 24 weeks) (n=33) versus sham injection (n=32) FU up to 52 weeks	BCVA (ETDRS letters): <table border="1" data-bbox="394 402 1430 1247"> <thead> <tr> <th></th> <th>Baseline</th> <th>30 weeks</th> <th>p</th> <th>52 weeks</th> <th>p</th> </tr> </thead> <tbody> <tr> <td colspan="6">BCVA (letters)</td> </tr> <tr> <td><i>PS 0.3 mg</i></td> <td>47.6</td> <td>+7.1</td> <td>NS, 0.09 vs sham</td> <td>+7.5</td> <td>NS vs sham</td> </tr> <tr> <td><i>PS 1 mg</i></td> <td>48.4</td> <td>+9.9</td> <td>0.02 vs sham</td> <td>+6.3</td> <td>NS vs sham</td> </tr> <tr> <td><i>Sham</i></td> <td>48.5</td> <td>-3.2</td> <td></td> <td>-2.4</td> <td></td> </tr> <tr> <td colspan="6">≥15 letters gained</td> </tr> <tr> <td><i>PS 0.3 mg</i></td> <td></td> <td>36%</td> <td colspan="3">NS, p=0.48</td> </tr> <tr> <td><i>PS 1 mg</i></td> <td></td> <td>39%</td> <td colspan="3"></td> </tr> <tr> <td><i>Sham</i></td> <td></td> <td>28%</td> <td colspan="3"></td> </tr> <tr> <td colspan="6">≥15 letters lost</td> </tr> <tr> <td><i>PS 0.3 mg</i></td> <td></td> <td>9%</td> <td colspan="3">0.03 vs sham</td> </tr> <tr> <td><i>PS 1 mg</i></td> <td></td> <td>6%</td> <td colspan="3">0.01 vs sham</td> </tr> <tr> <td><i>Sham</i></td> <td></td> <td>31%</td> <td colspan="3"></td> </tr> </tbody> </table> CRT (μm):		Baseline	30 weeks	p	52 weeks	p	BCVA (letters)						<i>PS 0.3 mg</i>	47.6	+7.1	NS, 0.09 vs sham	+7.5	NS vs sham	<i>PS 1 mg</i>	48.4	+9.9	0.02 vs sham	+6.3	NS vs sham	<i>Sham</i>	48.5	-3.2		-2.4		≥15 letters gained						<i>PS 0.3 mg</i>		36%	NS, p=0.48			<i>PS 1 mg</i>		39%				<i>Sham</i>		28%				≥15 letters lost						<i>PS 0.3 mg</i>		9%	0.03 vs sham			<i>PS 1 mg</i>		6%	0.01 vs sham			<i>Sham</i>		31%				No serious ocular adverse events up to week 30 No endophthalmitis, traumatic cataract or retinal detachment (30 weeks) No evidence of sustained effect on intraocular pressure (30 weeks) No evidence of increased risk of systemic adverse events (30 weeks)
	Baseline	30 weeks	p	52 weeks	p																																																																											
BCVA (letters)																																																																																
<i>PS 0.3 mg</i>	47.6	+7.1	NS, 0.09 vs sham	+7.5	NS vs sham																																																																											
<i>PS 1 mg</i>	48.4	+9.9	0.02 vs sham	+6.3	NS vs sham																																																																											
<i>Sham</i>	48.5	-3.2		-2.4																																																																												
≥15 letters gained																																																																																
<i>PS 0.3 mg</i>		36%	NS, p=0.48																																																																													
<i>PS 1 mg</i>		39%																																																																														
<i>Sham</i>		28%																																																																														
≥15 letters lost																																																																																
<i>PS 0.3 mg</i>		9%	0.03 vs sham																																																																													
<i>PS 1 mg</i>		6%	0.01 vs sham																																																																													
<i>Sham</i>		31%																																																																														

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events			
	Baseline	30 weeks	p	52 weeks	p				
	CRT								
	PS 0.3 mg	688	-243	NS, p=0.13	-295	<0.05 vs sham			
	PS 1 mg	632	-179	NS, p=0.06	-216				
	Sham	674	-148		-183				
	3 patients in the sham arm and 1 patient in each of the pegaptanib sodium arms developed ocular neovascularisation (p=0.29 (NS))								
RANIBIZUMAB									
CRUISE 2010 ff. ^{10;45;46}	BCVA (ETDRS letters):					6 months			
	Baseline	6 months	12 months (ran PRN)		24 months (ran PRN, HORIZON)	AE	Ran 0.3 mg	Ran 0.5 mg	Sham
0.3 mg intravitreal ranibizumab (monthly for 6 months)	BCVA (letters, 95% CI)								
	Ran 0.3 mg	47.4	+12.7 (9.9, 15.4), p<0.0001 vs sham	+13.9 SD15.2, p=0.0007 vs sham	+8.2	Any intraocular inflammation event	2.3 %	1.6%	3.9%
	Ran 0.5 mg	48.1	+14.9 (12.6, 17.2), p<0.0001 vs sham	+13.9 SD14.2, p=0.0006 vs sham	+12.0	Iridocyclitis	0	0	0
versus 0.5 mg intravitreal ranibizumab (monthly for 6 months)	Sham	49.2	+0.8 (-2.0, 3.6)	+7.3 SD15.9	+7.6	Iritis	1.5%	1.6%	2.3%
		SD14.7				Vitritis	0.8%	0.8%	1.6%
						Endophthalmitis	0	0	0

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				Adverse events											
versus sham	≥15 letters gained				Lens damage	0	0	0								
extension 6 to 12 months 0.3 or 0.5 mg ranibizumab PRN	Ran 0.3 mg	46.2%, p<0.0001 vs sham	47.0%	38.6%	Cataract	1.5%	1.6%	0								
	Ran 0.5 mg	47.7%, p<0.0001 vs sham	50.8%	45.1%	Iris neovascularisation	1.5%	0.8%	7.0%								
	Sham	16.9%	33.1%	38.3%	Neovascular glaucoma	0	0	1.6%								
extension ≥12 to 24 months 0.5 mg ranibizumab PRN	≥15 letters lost				Rhegmatogenous retinal detachment	0	0	0								
	Ran 0.3 mg	3.8%	3.8%	12.9%	Retinal tear	0	0	0								
	Ran 0.5 mg	1.5%	2.3%	5.9%	Vitreous haemorrhage	3.8%	5.4%	7.0%								
	Sham	15.4%	10.0%	13.3%	Systemic adverse events balanced across groups; 1 myocardial infarction in each group, 1 transient ischaemic attack and angina pectoris in the same person in ran 0.5 mg group											
	Subgroups				12 months, sham for months 6 to 12											
	Time of diagnosis (6 month outcomes): <3 months: +13.2 letters (both ran groups), ≥3 months: +10.5 letters (0.3 mg ran), +15.3 letters (0.5 mg ran), p=?				<table border="1"> <thead> <tr> <th>Ocular AE</th> <th>Ran 0.3 mg</th> <th>Ran 0.5 mg</th> <th>Sham</th> </tr> </thead> <tbody> <tr> <td>Any intraocular inflammation</td> <td>2.3 %</td> <td>1.6%</td> <td>1.8%</td> </tr> </tbody> </table>				Ocular AE	Ran 0.3 mg	Ran 0.5 mg	Sham	Any intraocular inflammation	2.3 %	1.6%	1.8%
Ocular AE	Ran 0.3 mg	Ran 0.5 mg	Sham													
Any intraocular inflammation	2.3 %	1.6%	1.8%													
	Mean change in BCVA was greater for patients with worse baseline BCVA and CRT >450 μm															
	CRT (μm) and anatomic															
	Baseline	6 months	12 months (ran PRN)	24 months (ran PRN, HORIZON)												

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				Adverse events				
	CRT (μm, 95% CI)				event				
	Ran 0.3 mg	679.9 SD 242.4	-433.7 (-484.9, -382.6), p<0.0001 vs sham	-462.1, p= NS vs sham	-370.9				
	Ran 0.5 mg	688.7 SD 253.1	-452.3 (-497.0, -407.6), p<0.0001 vs sham	-452.8, p=NS vs sham	-412.2				
	Sham	687.0 SD 237.6	-167.7 (-221.5 -114.0)	-427.2	-418.7				
	CRT \leq250 μm								
	Ran 0.3 mg		75.0%, p<0.0001 vs sham	75.8%	58.0%				
	Ran 0.5 mg		76.9%, p<0.0001 vs sham	77.7%	56.9%				
	Sham		23.1%	70.8%	70.2%				
	No retinal haemorrhages								
	Ran 0.3 mg		0.8%	31.5%	41.3%				
	Ran 0.5 mg		1.5%	39.3%	47.8%				
	Sham		1.5%	5.4%	36.7%				
	QoL				HORIZON, 12 to 24 months				
						AE	Ran 0.3/0.5	Ran 0.5	Sham/ran 0.5 mg
						Endophthalmitis	0	0	0
						Lens damage	0	0	0
						Cataract	3.8%	7.0%	1.8%
						Iris neovascularisation	1.5%	3.9%	1.8%
						Neovascular glaucoma	0	0.8%	0
						Rhegmatogenous retinal detachment	0	0	0
						Retinal tear	0	1.6%	1.8%
						Vitreous haemorrhage	5.3%	5.4%	1.8%
						Arterial thromboembolic events	0.8%	2.3%	0

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events			
	Baseline	6 months	p	12 months (ran PRN)	p	mg	mg	mg	
NEI-VFQ (95% CI)	Ran 0.3 mg	+7.1 (5.2, 9.0)	<0.05 vs sham	+7.1	NS vs sham	Any ocular AE	62.6%	66.7%	62.5%
	Ran 0.5 mg	+6.2 (4.3, 8.0)	<0.05 vs sham	+6.6	NS vs sham	Ocular AEs leading to discontinuation	1.9%	2.0%	0
	Sham	+2.8 (0.8, 4.7)		+5.0		Cataract	5.6%	5.1%	3.1%
						Ocular serious adverse events	9.3%	3.0%	5.2%
						Cystoid macular oedema	0.9%	0	0
						Endophthalmitis	1.9%	0	0
						IOP increased	0.9%	0	0
						Macular oedema	1.9%	2.0%	1.0%
						Ischaemic optic neuropathy	0.9%	0	0
						VA reduced	1.9%	1.0%	3.1%
						VA reduced transiently	0.9%	0	0
						Vitreous haemorrhage	0	0	1.0%
						Arterial thromboembolic	1.9%	3.0%	2.1%

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)	Adverse events																																																						
BEVACIZUMAB																																																								
<p>Epstein 2012⁴⁷⁻⁴⁹</p> <p>1.25 mg intravitreal bevacizumab (4 injections over 6 months) (n=30) versus sham injection (n=30)</p> <p>6 month open label extension (1.25 mg intravitreal bevacizumab (4 injections over 6 months) for all patients)</p>	<p>BCVA (ETDRS letters):</p> <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>24 weeks</th> <th>p</th> <th>48 weeks (bev/bev vs sham/bev)</th> <th>p</th> </tr> </thead> <tbody> <tr> <td>BCVA (letters)</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Bev</td> <td>44.4 SD15.3; 30% <34, 70% >34</td> <td>+14.1</td> <td><0.01</td> <td>+16.1</td> <td><0.05</td> </tr> <tr> <td>Sham</td> <td>43.9 SD16.0; 33.3% <34, 66.7% >34</td> <td>-2.0</td> <td></td> <td>+4.6</td> <td></td> </tr> <tr> <td>≥15 letters gained</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Bev</td> <td></td> <td>60%</td> <td>0.003</td> <td>60%</td> <td><0.05</td> </tr> <tr> <td>Sham</td> <td></td> <td>20%</td> <td></td> <td>33.3%</td> <td></td> </tr> <tr> <td>>15 letters lost</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Bev</td> <td></td> <td>6.7%</td> <td>NS, p=0.146</td> <td>6.7%</td> <td>NS</td> </tr> </tbody> </table>		Baseline	24 weeks	p	48 weeks (bev/bev vs sham/bev)	p	BCVA (letters)						Bev	44.4 SD15.3; 30% <34, 70% >34	+14.1	<0.01	+16.1	<0.05	Sham	43.9 SD16.0; 33.3% <34, 66.7% >34	-2.0		+4.6		≥15 letters gained						Bev		60%	0.003	60%	<0.05	Sham		20%		33.3%		>15 letters lost						Bev		6.7%	NS, p=0.146	6.7%	NS	<p>Adverse events:</p> <p>Neovascularisation: 16.7% (sham) versus 0 (bev) had developed iris rubeosis at week 24; iris rubeosis regressed in all patients at week 48, no new cases in either group</p> <p>No events of endophthalmitis, retinal tear, retinal detachment; no serious non-ocular adverse events</p>
	Baseline	24 weeks	p	48 weeks (bev/bev vs sham/bev)	p																																																			
BCVA (letters)																																																								
Bev	44.4 SD15.3; 30% <34, 70% >34	+14.1	<0.01	+16.1	<0.05																																																			
Sham	43.9 SD16.0; 33.3% <34, 66.7% >34	-2.0		+4.6																																																				
≥15 letters gained																																																								
Bev		60%	0.003	60%	<0.05																																																			
Sham		20%		33.3%																																																				
>15 letters lost																																																								
Bev		6.7%	NS, p=0.146	6.7%	NS																																																			

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)				Adverse events
	<i>Sham</i>	23.3%	6.7%		
	Subgroups				
	Disease duration	BCVA (letters)			
	<i>Bev <90 days</i>	+18.7	0.039		
	<i>Bev >90 days</i>	+9.8			
	Age	BCVA (letters)			
	<i><70 years</i>	+14.2	NS, >0.05		
	<i>>70 years</i>	+7.4			
	<i><70 years sham/bev</i>	-1.4	<0.003		
	<i>>70 years sham/bev</i>	+20.1			
	CRT (µm):				
	Baseline	24 weeks	p	48 weeks (bev/bev vs sham/bev)	p

Study	Clinical outcomes (BCVA, CRT; change from baseline at study end)					Adverse events
	CRT					
	<i>Bev/bev</i>	712 SD330	-426	<0.001	-435	NS, >0.05
	<i>Sham/bev</i>	729 SD195	-102		-404	
	No residual oedema (CRT <300 µm)					
	<i>Bev/bev</i>		86.7%	<0.001	83.3%	NS
	<i>Sham/bev</i>		20%		60%	

Abbreviations: AE – adverse event, BCVA – best corrected visual acuity, CI – confidence interval, CRT – central retinal thickness, CRVO – central retinal vein occlusion, ETDRS – Early Treatment Diabetic Retinopathy Study, FU – follow-up, IQR – interquartile range, IOP – intraocular pressure, mo – months, NR – not reported, NS – non-significant, OCT – optical coherence tomography, PRN – pro re nata (as needed), QoL – quality of life, SD – standard deviation

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

11 Table 3: Study quality

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
DEXAMETHASONE							
GENEVA 2010 ff.	Low	Low	Partial: patients and assessors of efficacy variables	Low: ITT analysis, 94% FU at 6 months	Low	Power: 81% power to detect difference in primary outcome with n=495 for each trial Similarity at baseline: yes	Allergan Inc.
TRIAMCINOLONE							
SCORE 2009 ff	Low	Unclear	Partial (physicians and patients masked to dose but not triamcinolone versus observation)	Low: ITT analysis, 83 to 90% FU at 12 months	Low	Power: 80% power to detect difference in primary outcome with n=486 (but only 271 randomised) Similarity at baseline: yes	National Eye Institute grants, Allergan

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
ROVO 2013	Low	Low	Unclear	Low: ITT analysis (?), 92% FU at 12 months	Low	<p><i>Power:</i> 80% power to detect difference in primary outcome with n=53 per group (but only 20 to 38 per group)</p> <p><i>Similarity at baseline:</i> unclear</p> <p><i>Other:</i> limited baseline data</p>	Jubiläumsfonds der Österreichischen Nationalbank, Ludwig Boltzmann Institute for Retinology and Biomicroscopic Laser Surgery (non-commercial)
AFLIBERCEPT							
COPERNICUS 2012	Low	Unclear	Low: double-blind	Low: ITT analysis, 89.9% assessed at primary end point	Low	<p><i>Power:</i> 90% power to detect difference in primary outcome with n=165</p> <p><i>Similarity at baseline:</i> yes</p>	Bayer HealthCare, Regeneron Pharmaceuticals

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
GALILEO 2012	Unclear	Unclear	Low: double-blind	Low: ITT analysis, 86% assessed at primary end point	Low	Power: 90% power to detect difference in primary outcome with n=150 Similarity at baseline: yes	Bayer HealthCare, Regeneron Pharmaceuticals
PEGAPTANIB							
Wroblewski 2009	Low	Low	Low: patients and ophthalmologist responsible for patients care and assessments	Low: ITT analysis, 7% withdrawals	Low	Power: 80% power to detect difference in primary outcome with n=30 per group Similarity at baseline: yes	Eyetech Inc, Pfizer Inc.
RANIBIZUMAB							
CRUISE 2010 ff	Low	Unclear	Low: patients and evaluating examiners, injecting physicians masked to dose	Low: ITT analysis, 88.5 to 97.7% completed 6 months	Low	Power: not reported Similarity at baseline: yes	Genentech Inc.

Study (author and year)	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting	Free of other bias (e.g. similarity at baseline, power assessment)	Funder
BEVACIZUMAB							
Epstein 2012	Unclear	Low	Low: patients, outcome assessors	Low: ITT analysis; missing data for 2 patients (primary endpoint)	Low	Power: 80% power to detect difference in primary outcome with n=24 per group Similarity at baseline: yes	Unclear; authors are consultants for Allergan, Novartis, Alcon, Bayer

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

12
13

14 Table 4: On-going trials

Study	Participants and baseline values	Intervention / Outcomes
<p data-bbox="176 370 342 394">MINOCYCLINE</p> <p data-bbox="176 431 806 456">http://clinicaltrials.gov/ct2/show/study/NCT01468844</p> <p data-bbox="176 492 226 516">USA</p> <p data-bbox="176 607 726 667">Study aim: to test the safety and effectiveness of minocycline as a treatment for CRVO</p> <p data-bbox="176 699 464 724">Design: RCT, double-blind</p> <p data-bbox="176 756 426 781">Follow-up: 24 months</p>	<p data-bbox="829 431 905 456">N: ~20</p> <p data-bbox="829 548 1419 643">Inclusion criteria: >18 years, macular oedema secondary to CRVO, CRT >350 µm, media clarity and pupillary dilatation sufficient for fundus photographs</p> <p data-bbox="829 675 1451 1003">Exclusion criteria: macular oedema due to causes other than CRVO, history of recurrent RVO or RVO >18 months, any other ocular condition that could affect macular oedema or BCVA, substantial cataract, photocoagulation within 4 months before study, pars plana vitrectomy within 6 months, major ocular surgery within 3 months, study eye treated with intravitreal or periocular steroid injections within 3 months, study eye treated with intravitreal anti-VEGF agents within 28 days; significant systemic disease (details given)</p>	<p data-bbox="1478 431 1902 558">Mino: 100 mg oral minocycline twice daily over 24 months; monthly bevacizumab injection over 3 months, then PRN</p> <p data-bbox="1478 591 1902 685">Placebo: oral placebo twice daily over 24 months; monthly bevacizumab injection over 3 months, then PRN</p> <p data-bbox="1478 776 1850 836">Primary end point: BCVA over 12 months</p> <p data-bbox="1478 868 1877 928">Other outcomes: number of bevacizumab injections, CRT, safety</p> <p data-bbox="1478 961 1877 1021">Outcome assessment: 6, 12, 18, 24 months</p>

Study	Participants and baseline values	Intervention / Outcomes
BEVACIZUMAB / TRIAMCINOLONE		
<p data-bbox="176 370 684 399">http://clinicaltrials.gov/show/NCT00566761</p> <p data-bbox="176 431 260 456">Mexico</p> <p data-bbox="176 548 779 675">Study aim: to assess if treatment of macular oedema secondary to CRVO is more effective with combined therapy of bevacizumab and triamcinolone compared to bevacizumab alone</p> <p data-bbox="176 708 543 737">Design: RCT, open-label, phase 4</p> <p data-bbox="176 769 426 799">Follow-up: 12 months</p>	<p data-bbox="829 375 905 399">N: ~10</p> <p data-bbox="829 492 1451 553">Inclusion criteria: macular oedema secondary to CRVO; BCVA <20/40; CRT >250 µm (OCT)</p> <p data-bbox="829 643 1444 769">Exclusion criteria: diabetic retinopathy or other retinopathy; media opacity that does not allow follow-up; steroid responder; diagnosed glaucoma or IOP > 21 mmHg</p>	<p data-bbox="1478 375 1881 436">Bev: bevacizumab 2.5 mg for (3 applications, administered monthly)</p> <p data-bbox="1478 469 1913 563">Bev/Tria: bevacizumab 2.5 mg + triamcinolone 4 mg first dose followed by two doses of bevacizumab alone</p> <p data-bbox="1478 651 1850 712">Primary end point: BCVA over 12 months</p> <p data-bbox="1478 745 1793 807">Other outcomes: treatment complications</p> <p data-bbox="1478 839 1860 901">Outcome assessment: 3, 6 and 12 months</p>
RANIBIZUMAB		

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Study	Participants and baseline values	Intervention / Outcomes
<p>http://clinicaltrials.gov/show/NCT01123564</p> <p>Hungary</p> <p>Study aim: to assess if ranibizumab (Lucentis) injection applied into the eye is superior to conventional treatment concerning the prevention of visual loss in patients having clinically significant macular oedema secondary to retinal vein occlusion</p> <p>Design: RCT, open-label, phase 2</p> <p>Follow-up: 12 months</p>	<p>N: ~40</p> <p>Inclusion criteria: >18 years, macular oedema persisting for >3 months despite conventional medication; CRVO confirmed by slit-lamp biomicroscopy and fluorescein angiography (FLAG); patient in ranibizumab group do not receive macular laser treatment; CRT > 280 µm and/or retinal thickness is >330 µm at any region of the macula; baseline VA <64 ETDRS letters (or 0.4 decimal equivalent)</p> <p>Exclusion criteria: diabetes mellitus; additional vitreoretinal diseases; history of pars plana vitrectomy; previous macular grid laser treatment; intravitreal triamcinolone acetonide treatment; complicated cataract surgery; advanced glaucomatous damage of optic nerve head; cataract (except mild, defined as grade 1 nuclear sclerosis and/or grade 1 posterior subcapsular cataract); age-related macular degeneration; pregnancy and lactation; women in childbearing potential who are not using double safe contraception</p>	<p>Rani: intravitreal ranibizumab, applied monthly in the first 3 months, and after this only if visual acuity (VA) decreases with more than 5 letters at any monthly visits</p> <p>Laser: Argon laser treatment; conventional grid pattern argon laser treatment and panretinal argon laser photocoagulation in an as needed basis</p> <p>Primary end point: BCVA over 12 months</p> <p>Other outcomes: CRT</p> <p>Outcome assessment: monthly visits</p>

15 **References**

- 16
- 17 (1) Deramo VA, Cox TA, Syed AB, Lee PP, Fekrat S. Vision-related quality of life in people with
18 central retinal vein occlusion using the 25-item National Eye Institute Visual Function
19 Questionnaire. *Arch Ophthalmol* 2003; 121(9):1297-1302.
- 20 (2) McIntosh RL, Rogers SL, Lim L, Cheung N, Wang JJ, Mitchell P et al. Natural history of
21 central retinal vein occlusion: an evidence-based systematic review. *Ophthalmology* 2010;
22 117(6):1113-1123.
- 23 (3) Mitchell P, Smith W, Chang A. Prevalence and associations of retinal vein occlusion in
24 Australia. The Blue Mountains Eye Study. *Arch Ophthalmol* 1996; 114(10):1243-1247.
- 25 (4) Rogers S, McIntosh RL, Cheung N, Lim L, Wang JJ, Mitchell P et al. The prevalence of retinal
26 vein occlusion: pooled data from population studies from the United States, Europe, Asia,
27 and Australia. *Ophthalmology* 2010; 117(2):313-319.
- 28 (5) The Royal College of Ophthalmology. Interim guidelines for management of retinal vein
29 occlusion. [http://www.rcophth.ac.uk/core/core_picker/download](http://www.rcophth.ac.uk/core/core_picker/download.asp?id=728&filetitle=Interim+Guidelines+for+Management+of+Retinal+Vein+Occlusion+2010)
30 [asp?id=728&filetitle=Interim+Guidelines+for+Management+of+Retinal+Vein+Occlusion+2](http://www.rcophth.ac.uk/core/core_picker/download.asp?id=728&filetitle=Interim+Guidelines+for+Management+of+Retinal+Vein+Occlusion+2010)
31 010 [2010 [cited 2013 Sept. 7];
- 32 (6) Hayreh SS, Podhajsky PA, Zimmerman MB. Natural history of visual outcome in central
33 retinal vein occlusion. *Ophthalmology* 2011; 118(1):119-133.
- 34 (7) Kiire CA, Chong NV. Managing retinal vein occlusion. *BMJ* 2012; 344:e499.
- 35 (8) The Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema
36 in branch vein occlusion. *Am J Ophthalmol* 1984; 98(3):271-282.
- 37 (9) The Central Vein Occlusion Study Group. Evaluation of grid pattern photocoagulation for
38 macular edema in central vein occlusion. *Ophthalmology* 1995; 102(10):1425-1433.
- 39 (10) Brown DM, Campochiaro PA, Singh RP, Li Z, Gray S, Saroj N et al. Ranibizumab for macular
40 edema following central retinal vein occlusion: six-month primary end point results of a
41 phase III study. *Ophthalmology* 2010; 117(6):1124-1133.
- 42 (11) Haller JA, Bandello F, Belfort R, Jr., Blumenkranz MS, Gillies M, Heier J et al. Randomized,
43 sham-controlled trial of dexamethasone intravitreal implant in patients with macular
44 edema due to retinal vein occlusion. *Ophthalmology* 2010; 117(6):1134-1146.
- 45 (12) Cunningham MA, Edelman JL, Kaushal S. Intravitreal steroids for macular edema: the past,
46 the present, and the future. *Surv Ophthalmol* 2008; 53(2):139-149.
- 47 (13) Miller JW, Le CJ, Strauss EC, Ferrara N. Vascular endothelial growth factor A in intraocular
48 vascular disease. *Ophthalmology* 2013; 120(1):106-114.
- 49 (14) Ford JA, Lois N, Royle P, Clar C, Shyangdan D, Waugh N. Current treatments in diabetic
50 macular oedema: systematic review and meta-analysis. *BMJ Open* 2013; 3(3).

- 1
2
3 51 (15) Shyangdan D, Cummins E, Lois N, Royle P, Waugh N. Dexamethasone implants in the
4 52 treatment of macular oedema due to retinal vein occlusion: a single technology appraisal.
5 53 <http://www.nice.org.uk/nicemedia/live/13037/52883/52883.pdf> . 2010. Aberdeen HTA
6 54 Group.
7 55
- 8 56 (16) Higgins J, Altman D, Gøtzsche PC, Jüni P, Moher D, Oxman AD et al. The Cochrane
9 57 Collaboration's tool for assessing risk of bias in randomised trials. *British Medical Journal*
10 58 2011; 343:d5928.
- 11
12
13 59 (17) Haller JA, Bandello F, Belfort R, Jr., Blumenkranz MS, Gillies M, Heier J et al.
14 60 Dexamethasone intravitreal implant in patients with macular edema related to branch or
15 61 central retinal vein occlusion twelve-month study results. *Ophthalmology* 2011;
16 62 118(12):2453-2460.
- 17
18 63 (18) Yeh WS, Haller JA, Lanzetta P, Kuppermann BD, Wong TY, Mitchell P et al. Effect of the
19 64 duration of macular edema on clinical outcomes in retinal vein occlusion treated with
20 65 dexamethasone intravitreal implant. *Ophthalmology* 2012; 119(6):1190-1198.
- 21
22 66 (19) Bhavsar AR, Ip MS, Glassman AR, DRCRnet and the SCORE Study Groups. The risk of
23 67 endophthalmitis following intravitreal triamcinolone injection in the DRCRnet and SCORE
24 68 clinical trials. *American Journal of Ophthalmology* 2007; 144(3):454-456.
- 25
26 69 (20) Blodi BA, Domalpally A, Scott IU, Ip MS, Oden NL, Elledge J et al. Standard Care vs
27 70 Corticosteroid for Retinal Vein Occlusion (SCORE) Study system for evaluation of
28 71 stereoscopic color fundus photographs and fluorescein angiograms: SCORE Study Report
29 72 9. *Archives of Ophthalmology* 2010; 128(9):1140-1145.
- 30
31 73 (21) Chan CK, Ip MS, VanVeldhuisen PC, Oden NL, Scott IU, Tolentino MJ et al. SCORE Study
32 74 report #11: incidences of neovascular events in eyes with retinal vein occlusion.
33 75 *Ophthalmology* 2011; 118(7):1364-1372.
- 34
35
36 76 (22) Ip M, Oden N, VanVeldhuisen P, Scott I, Blodi B. The Standard Care vs. Corticosteroid for
37 77 Retinal Vein Occlusion Study: Design and Baseline Characteristics. *American Academy of*
38 78 *Ophthalmology* 2008;260.
- 39
40 79 (23) Ip MS, Scott IU, VanVeldhuisen PC, Oden NL, Blodi BA, Fisher M et al. A randomized trial
41 80 comparing the efficacy and safety of intravitreal triamcinolone with observation to treat
42 81 vision loss associated with macular edema secondary to central retinal vein occlusion: the
43 82 Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5. *Archives*
44 83 *of Ophthalmology* 2009; 127(9):1101-1114.
- 45
46 84 (24) Ip MS, Oden NL, Scott IU, VanVeldhuisen PC, Blodi BA, Figueroa M et al. SCORE Study
47 85 report 3: study design and baseline characteristics. *Ophthalmology* 2009; 116(9):1770-
48 86 1777.
- 49
50
51 87 (25) Myers D, Blodi B, Ip M, Scott I, Warren K. Reading Center Evaluation of OCT Images From
52 88 Patients Enrolled in the Standard Care vs. Corticosteroid for Retinal Vein Occlusion
53 89 (SCORE) Study. *IOVS* 2006; 47:ARVO.
- 54
55 90 (26) Oden NL, Veldhuisen PC, Scott IU, Ip MS, Blodi BA. Temporal Variability of OCT in Retinal
56 91 Vein Occlusion Participants in the SCORE Study. *IOVS* 2007; 48:ARVO.

- 1
2
3 92 (27) Scott IU, VanVeldhuisen PC, Oden NL, Ip MS, Blodi BA, Jumper JM et al. SCORE Study
4 93 report 1: baseline associations between central retinal thickness and visual acuity in
5 94 patients with retinal vein occlusion. *Ophthalmology* 2009; 116(3):504-512.
- 7 95 (28) Scott IU, Blodi BA, Ip MS, VanVeldhuisen PC, Oden NL, Chan CK et al. SCORE Study Report
8 96 2: Interobserver agreement between investigator and reading center classification of
9 97 retinal vein occlusion type. *Ophthalmology* 2009; 116(4):756-761.
- 11 98 (29) Scott IU, Oden NL, VanVeldhuisen PC, Ip MS, Blodi BA, Antoszyk AN et al. SCORE Study
12 99 Report 7: incidence of intravitreal silicone oil droplets associated with staked-on vs luer
13 100 cone syringe design. *American Journal of Ophthalmology* 2009; 148(5):725-732.
- 16 101 (30) Scott IU, VanVeldhuisen PC, Oden NL, Ip MS, Blodi BA, Hartnett ME et al. Baseline
17 102 predictors of visual acuity and retinal thickness outcomes in patients with retinal vein
18 103 occlusion: Standard Care Versus Corticosteroid for Retinal Vein Occlusion Study report 10.
19 104 *Ophthalmology* 2011; 118(2):345-352.
- 21 105 (31) Scott IU, VanVeldhuisen PC, Oden NL, Ip MS, Domalpally A, Doft BH et al. Baseline
22 106 characteristics and response to treatment of participants with hemiretinal compared with
23 107 branch retinal or central retinal vein occlusion in the Standard Care vs Corticosteroid for
24 108 REtinal Vein Occlusion (SCORE) study: SCORE Study Report 14. *Archives of Ophthalmology*
25 109 2012; 130(12):1517-1524.
- 27 110 (32) Warren K, Blodi BA, Oden N, Veldhuisen P, Scott IU, Ip M. Reading Center Evaluation of
28 111 Baseline Retinal Images in the Standard Care vs. Corticosteroid for Retinal Vein Occlusion
29 112 (SCORE) Study. *Iovs* 2008;ARVO.
- 31 113 (33) Aggermann T, Brunner S, Krebs I, Haas P, Womastek I, Brannath W et al. A prospective,
32 114 randomised, multicenter trial for surgical treatment of central retinal vein occlusion:
33 115 results of the Radial Optic Neurotomy for Central Vein Occlusion (ROVO) study group.
34 116 *Graefes Arch Clin Exp Ophthalmol* 2013; 251(4):1065-1072.
- 37 117 (34) Boyer D, Heier J, Brown DM, Clark WL, Vitti R, Berliner AJ et al. Vascular endothelial
38 118 growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-
39 119 month results of the phase 3 COPERNICUS study. *Ophthalmology* 2012; 119(5):1024-1032.
- 41 120 (35) Brown DM, Heier JS, Clark WL, Boyer DS, Vitti R, Berliner AJ et al. Intravitreal aflibercept
42 121 injection for macular edema secondary to central retinal vein occlusion: 1-Year Results
43 122 From the Phase 3 COPERNICUS Study. *American Journal of Ophthalmology* 2013;
44 123 155(3):429-437.
- 46 124 (36) Gillies M. Intravitreal vegf trap-eye in central retinal vein occlusion: Results of the phase 3
47 125 copernicus and galileo studies. *Clinical and Experimental Ophthalmology* 2012; 40:44.
- 49 126 (37) Holz FG, Roider J, Ogura Y, Korobelnik JF, Simader C, Groetzbach G et al. VEGF Trap-Eye for
50 127 macular oedema secondary to central retinal vein occlusion: 6-month results of the phase
51 128 III GALILEO study. *British Journal of Ophthalmology* 2013; 97(3):278-284.
- 53 129 (38) Ciulla TA. Treatment of Macular Edema Following Central Retinal Vein Occlusion With
54 130 Pegaptanib Sodium (Macugen): A One-Year Study. *American Academy of Ophthalmology*
55 131 2007;199.

- 1
2
3 132 (39) Csaky KG. Pegaptanib (Macugen) for Macular Edema in Central Retinal Vein Occlusion:
4 133 Early OCT Results and Effect of Therapy Reinitiation. *American Academy of Ophthalmology*
5 134 2007;269.
- 6
7 135 (40) Patel SS. Pegaptanib Sodium for the Treatment of Macular Edema Following Central
8 136 Retinal Vein Occlusion (CRVO): Anatomical Outcomes. *Iovs* 2007; 48:ARVO.
- 9
10 137 (41) Wells JA. Pegaptanib Sodium for Treatment of Macular Edema Secondary to Central
11 138 Retinal Vein Occlusion (CRVO). *Iovs* 2006; 47:ARVO.
- 12
13 139 (42) Wells JA. Safety and Efficacy of Pegaptanib Sodium in Treating Macular Edema Secondary
14 140 to Central Retinal Vein Occlusion. *American Academy of Ophthalmology* 2006;288.
- 15
16 141 (43) Wells JA, Wroblewski JJ. Pegaptanib Sodium for the Treatment of Macular Edema
17 142 Following Central Retinal Vein Occlusion (CRVO): Functional Outcomes. *Iovs* 2007;
18 143 48:ARVO.
- 19
20 144 (44) Wroblewski JJ, Wells JA, III, Adamis AP, Buggage RR, Cunningham ET, Jr., Goldbaum M et
21 145 al. Pegaptanib sodium for macular edema secondary to central retinal vein occlusion.
22 146 *Archives of Ophthalmology* 2009; 127(4):374-380.
- 23
24 147 (45) Campochiaro PA, Brown DM, Awh CC, Lee SY, Gray S, Saroj N et al. Sustained benefits from
25 148 ranibizumab for macular edema following central retinal vein occlusion: twelve-month
26 149 outcomes of a phase III study. *Ophthalmology* 2011; 118(10):2041-2049.
- 27
28 150 (46) Heier JS, Campochiaro PA, Yau L, Li Z, Saroj N, Rubio RG et al. Ranibizumab for macular
29 151 edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial.
30 152 *Ophthalmology* 2012; 119(4):802-809.
- 31
32 153 (47) Epstein D, Algvere P, Von WG, Seregard S, Kvanta A. Long-term benefit from bevacizumab
33 154 for macular edema in central retinal vein occlusion: 12-month results of a prospective
34 155 study. *Acta Ophthalmologica* 2012; 90:48.
- 35
36 156 (48) Epstein DL, Algvere PV, Von WG, Seregard S, Kvanta A. Benefit from bevacizumab for
37 157 macular edema in central retinal vein occlusion: twelve-month results of a prospective,
38 158 randomized study. *Ophthalmology* 2012; 119(12):2587-2591.
- 39
40 159 (49) Epstein DL, Algvere PV, Von WG, Seregard S, Kvanta A. Bevacizumab for macular edema in
41 160 central retinal vein occlusion: a prospective, randomized, double-masked clinical study.
42 161 *Ophthalmology* 2012; 119(6):1184-1189.
- 43
44 162 (50) Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and
45 163 bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011;
46 164 364(20):1897-1908.
- 47
48 165 (51) Campbell RJ, Gill SS, Bronskill SE, Paterson JM, Whitehead M, Bell CM. Adverse events with
49 166 intravitreal injection of vascular endothelial growth factor inhibitors: nested case-control
50 167 study. *BMJ* 2012; 345:e4203.
- 51
52 168 (52) Curtis LH, Hammill BG, Schulman KA, Cousins SW. Risks of mortality, myocardial infarction,
53 169 bleeding, and stroke associated with therapies for age-related macular degeneration.
54 170 *Archives of Ophthalmology* 2010; 128(10):1273-1279.

- 1
2
3 171 (53) Hwang DJ, Kim YW, Woo SJ, Park KH. Comparison of systemic adverse events associated
4 172 with intravitreal anti-VEGF injection: ranibizumab versus bevacizumab. *J Korean Med Sci*
5 173 2012; 27(12):1580-1585.
- 6
7 174 (54) Sharma S, Johnson D, Abouammoh M, Hollands S, Brissette A. Rate of serious adverse
8 175 effects in a series of bevacizumab and ranibizumab injections. *Can J Ophthalmol* 2012;
9 176 47(3):275-279.
- 10
11 177 (55) Micieli JA, Micieli A, Smith AF. Identifying systemic safety signals following intravitreal
12 178 bevacizumab: systematic review of the literature and the Canadian Adverse Drug Reaction
13 179 Database. *Can J Ophthalmol* 2010; 45(3):231-238.
- 14
15
16 180 (56) Choi DY, Ortube MC, McCannel CA, Sarraf D, Hubschman JP, McCannel TA et al. Sustained
17 181 elevated intraocular pressures after intravitreal injection of bevacizumab, ranibizumab,
18 182 and pegaptanib. *Retina* 2011; 31(6):1028-1035.
- 19
20 183 (57) Good TJ, Kimura AE, Mandava N, Kahook MY. Sustained elevation of intraocular pressure
21 184 after intravitreal injections of anti-VEGF agents. *Br J Ophthalmol* 2011; 95(8):1111-1114.
- 22
23 185 (58) Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S et al.
24 186 Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration:
25 187 one-year findings from the IVAN randomized trial. *Ophthalmology* 2012; 119(7):1399-
26 188 1411.
- 27
28 189 (59) Ford JA, Elders A, Shyangdan D, Royle P, Waugh N. The relative clinical effectiveness of
29 190 ranibizumab and bevacizumab in diabetic macular oedema: an indirect comparison in a
30 191 systematic review. *BMJ* 2012; 345:e5182.
- 31
32 192 (60) Stewart MW. Aflibercept (VEGF Trap-eye): the newest anti-VEGF drug. *Br J Ophthalmol*
33 193 2012; 96(9):1157-1158.
- 34
35 194 (61) Braithwaite T, Nanji AA, Greenberg PB. Anti-vascular endothelial growth factor for macular
36 195 edema secondary to central retinal vein occlusion. *Cochrane Database Syst Rev*
37 196 2010;(10):CD007325.
- 38
39 197 (62) Gewaily D, Greenberg PB. Intravitreal steroids versus observation for macular edema
40 198 secondary to central retinal vein occlusion. *Cochrane Database Syst Rev*
41 199 2009;(1):CD007324.
- 42
43
44 200 (63) Lazo-Langner A, Hawel J, Ageno W, Kovacs MJ. Low molecular weight heparin for the
45 201 treatment of retinal vein occlusion: a systematic review and meta-analysis of randomized
46 202 trials. *Haematologica* 2010; 95(9):1587-1593.
- 47
48 203 (64) Squizzato A, Manfredi E, Bozzato S, Dentali F, Ageno W. Antithrombotic and fibrinolytic
49 204 drugs for retinal vein occlusion: a systematic review and a call for action. *Thromb Haemost*
50 205 2010; 103(2):271-276.
- 51
52
53 207 (65) [Pielen A, Feltgen N, Isserstedt C, Callizo J, Junker B, Schmuicher C. Efficacy and safety of
54 208 intravitreal Therapy in macular edema due to branch and central retinal vein occlusion: a
55 209 systematic review. *PLoS One* 2013; DOI: 10.1371/journal.pone.0078538](#)
- 56 210
57 211
58 212

1
2
3 213 Appendix 1: Search strategy

4
5 214 **CRVO: Clinical effectiveness search for RCTs and SRs**

6
7 215

8
9 216 **Ovid MEDLINE(R) 1946 to March Week 1 2013, searched on 20 March 2013**

10
11 1 CRVO.mp.

12
13 2 Retinal Vein Occlusion/

14
15 3 retinal vein occlusion.mp.

16
17 4 retinal vein obstruction.mp.

18
19 5 retinal venous occlusion.mp.

20
21 6 retinal venous obstruction.mp.

22
23 7 retina*.mp.

24
25 8 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central
26
27 venous obstruction").mp.

28
29 9 7 and 8

30
31 10 1 or 2 or 3 or 4 or 5 or 6 or 9

32
33 11 randomized controlled trial.pt.

34
35 12 (random* or "controlled trial*" or "clinical trial*" or rct).tw.

36
37 13 11 or 12

38
39 14 (metaanalys* or "meta analys*" or "meta-analys*").tw.

40
41 15 "systematic review*".tw.

42
43 16 meta analysis.pt.

44
45 17 14 or 15 or 16

46
47 18 10 and 13

48
49 19 10 and 17

50
51 20 18 or 19

52
53 21 limit 20 to yr="2005 -Current"

1
2
3 217
4
5 218
6
7 219 **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations March 19, 2013, searched on 20**
8 220 **March 2013**
9

10 1 CRVO.mp.
11

12 2 retinal vein occlusion.mp.
13

14 3 retinal vein obstruction.mp.
15

16 4 retinal venous occlusion.mp.
17

18 5 retinal venous obstruction.mp.
19

20 6 retina*.mp.
21

22 7 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central
23 venous obstruction").mp.
24

25 8 6 and 7
26

27 9 1 or 2 or 3 or 4 or 5 or 8
28

29 10 (random* or "controlled trial*" or "clinical trial*" or rct).tw.
30

31 11 (metaanalys* or "meta analys*" or "meta-analys*").tw.
32

33 12 "systematic review*".tw.
34

35 13 11 or 12
36

37 14 9 and 10
38

39 15 9 and 13
40

41 16 14 or 15
42
43
44
45

46 221
47

48 222
49

50 223 **Embase 1980 to 2013 Week 11, searched on 20 March 2013**
51

52 1 CRVO.mp.
53

54 2 Retina Vein Occlusion/
55
56
57
58
59
60

- 1
2
3 3 Central Retina Vein Occlusion/
4
5 4 retinal vein occlusion.mp.
6
7 5 retinal vein obstruction.mp.
8
9
10 6 retinal venous occlusion.mp.
11
12 7 retinal venous obstruction.mp.
13
14 8 retina*.mp.
15
16 9 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central
17 venous obstruction").mp.
18
19
20 10 8 and 9
21
22 11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 10
23
24 12 randomized controlled trial/
25
26 13 (random* or "controlled trial*" or "clinical trial*" or rct).tw.
27
28
29 14 12 or 13
30
31 15 systematic review/
32
33 16 meta analysis/
34
35 17 (metaanalys* or "meta analys*" or "meta-analys*").tw.
36
37
38 18 "systematic review*".tw.
39
40 19 15 or 16 or 17 or 18
41
42 20 11 and 14
43
44 21 11 and 19
45
46
47 22 20 or 21
48
49 23 limit 22 to yr="2005 -Current"
50
51 224
52
53 225 **Cochrane Library (including CDSR, CENTRAL, DARE, HTA, NHS EED), searched on 20 March 2013**
54
55 226 #1 CRVO
56
57 227 #2 MeSH descriptor: [Retinal Vein Occlusion] this term only
58
59
60

1
2
3 228 #3 "retinal vein occlusion"
4
5 229 #4 "retinal vein obstruction"
6
7 230 #5 "retinal venous occlusion"
8
9 231 #6 "retinal venous obstruction"
10
11 232 #7 retina*
12 233 #8 "central vein occlusion" or "central vein obstruction" or "central venous occlusion" or
13 234 "central venous obstruction"
14
15 235 #9 #7 and #8
16
17 236 #10 #1 or #2 or #3 or #4 or #5 or #6 or #9
18
19 237 #11 #10 from 2005
20
21 238
22
23 239
24
25 240
26
27 241
28
29 242
30
31 243
32
33 244
34
35 245
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	68-71
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	23
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	25-35
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	56-59
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Appendix 1: Search strategy

CRVO: Clinical effectiveness search for RCTs and SRs**Ovid MEDLINE(R) 1946 to March Week 1 2013, searched on 20 March 2013**

- 1 CRVO.mp.
- 2 Retinal Vein Occlusion/
- 3 retinal vein occlusion.mp.
- 4 retinal vein obstruction.mp.
- 5 retinal venous occlusion.mp.
- 6 retinal venous obstruction.mp.
- 7 retina*.mp.
- 8 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction").mp.
- 9 7 and 8
- 10 1 or 2 or 3 or 4 or 5 or 6 or 9
- 11 randomized controlled trial.pt.
- 12 (random* or "controlled trial*" or "clinical trial*" or rct).tw.
- 13 11 or 12
- 14 (metaanalys* or "meta analys*" or "meta-analys*").tw.
- 15 "systematic review*".tw.
- 16 meta analysis.pt.
- 17 14 or 15 or 16
- 18 10 and 13
- 19 10 and 17

1
2
3 20 18 or 19
4
5

6 21 limit 20 to yr="2005 -Current"
7
8
9

10
11 **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations March 19, 2013, searched on 20 March**
12 **2013**
13
14

15 1 CRVO.mp.
16

17 2 retinal vein occlusion.mp.
18

19 3 retinal vein obstruction.mp.
20

21 4 retinal venous occlusion.mp.
22

23 5 retinal venous obstruction.mp.
24

25 6 retina*.mp.
26

27 7 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central
28 venous obstruction").mp.
29

30 8 6 and 7
31

32 9 1 or 2 or 3 or 4 or 5 or 8
33

34 10 (random* or "controlled trial*" or "clinical trial*" or rct).tw.
35

36 11 (metaanalys* or "meta analys*" or "meta-analys*").tw.
37

38 12 "systematic review*".tw.
39

40 13 11 or 12
41

42 14 9 and 10
43

44 15 9 and 13
45

46 16 14 or 15
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Embase 1980 to 2013 Week 11, searched on 20 March 2013

- 1 CRVO.mp.
- 2 Retina Vein Occlusion/
- 3 Central Retina Vein Occlusion/
- 4 retinal vein occlusion.mp.
- 5 retinal vein obstruction.mp.
- 6 retinal venous occlusion.mp.
- 7 retinal venous obstruction.mp.
- 8 retina*.mp.
- 9 ("central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central venous obstruction").mp.
- 10 8 and 9
- 11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 10
- 12 randomized controlled trial/
- 13 (random* or "controlled trial*" or "clinical trial*" or rct).tw.
- 14 12 or 13
- 15 systematic review/
- 16 meta analysis/
- 17 (metaanalys* or "meta analys*" or "meta-analys*").tw.
- 18 "systematic review*".tw.
- 19 15 or 16 or 17 or 18
- 20 11 and 14
- 21 11 and 19

1
2
3 22 20 or 21
4
5

6 23 limit 22 to yr="2005 -Current"
7
8
9

10 **Cochrane Library (including CDSR, CENTRAL, DARE, HTA, NHS EED), searched on 20 March 2013**
11

12 #1 CRVO
13

14 #2 MeSH descriptor: [Retinal Vein Occlusion] this term only
15

16 #3 "retinal vein occlusion"
17

18 #4 "retinal vein obstruction"
19

20 #5 "retinal venous occlusion"
21

22 #6 "retinal venous obstruction"
23

24 #7 retina*
25

26 #8 "central vein occlusion" or "central vein obstruction" or "central venous occlusion" or "central
27 venous obstruction"
28

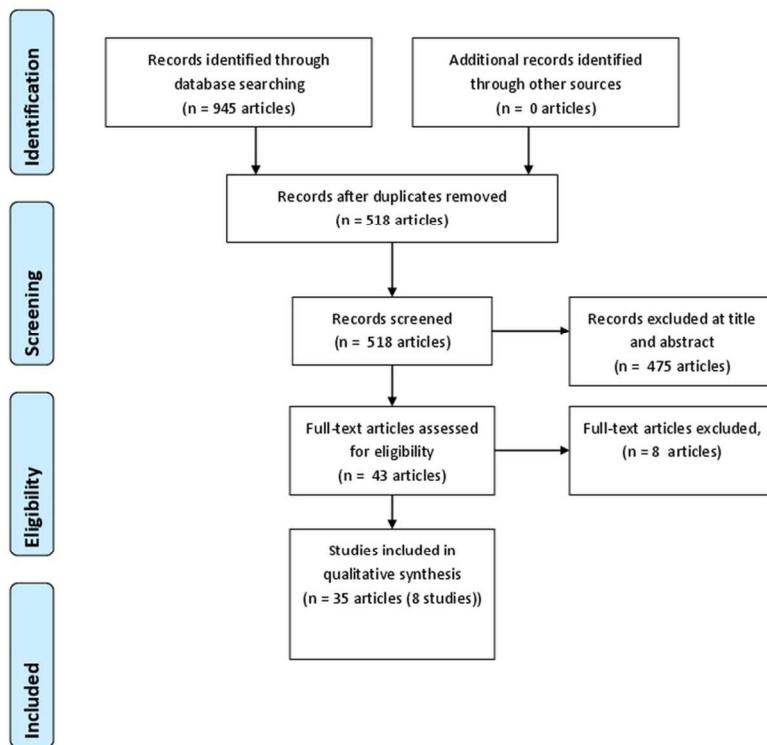
29 #9 #7 and #8
30

31 #10 #1 or #2 or #3 or #4 or #5 or #6 or #9
32

33 #11 #10 from 2005
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

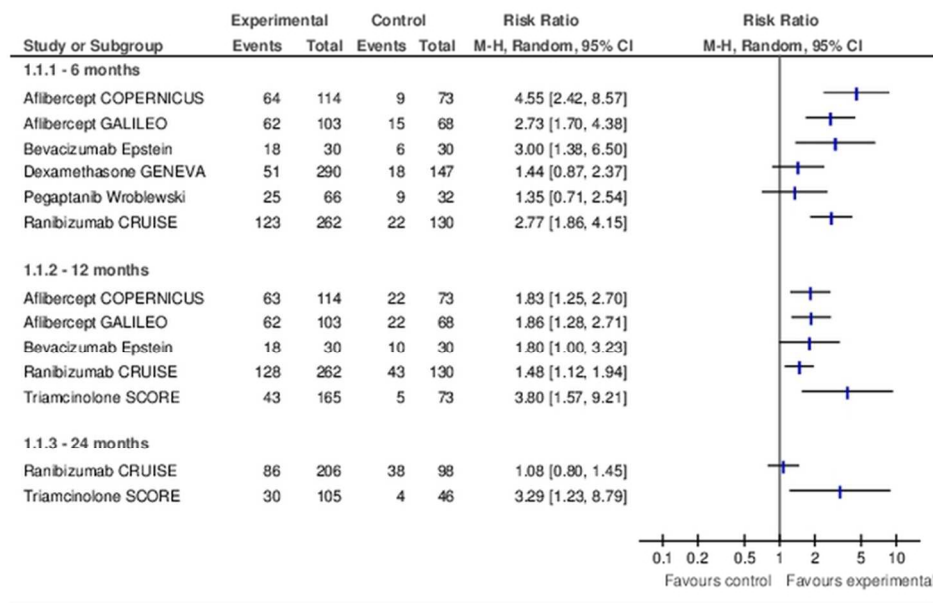
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1: PRISMA statement



90x116mm (300 x 300 DPI)

Figure 2. Study results for the primary outcome (≥ 15 ETDRS letter gain).



74x57mm (300 x 300 DPI)