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Corticosteroid implants for chronic non-infectious uveitis (Review)

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[Intervention Review]

Corticosteroid implants for chronic non-infectious uveitis

Amit Reddy[1], Su-Hsun Liu[1,2], Christopher J Brady[3,4], Pamela C Sieving[5], Alan G Palestine[1]

[1]Department of Ophthalmology, University of Colorado Anschutz Medical Campus, School of Medicine, Aurora, Colorado, USA. [2]Department of Epidemiology, University of Colorado Anschutz Medical Campus, School of Public Health, Aurora, Colorado, USA. [3]Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. [4]Surgery, Division of Ophthalmology, University of Vermont, Burlington, Vermont, USA. [5]Special Volunteer, National Eye Institute, Sacramento, California, USA

Contact: Amit Reddy, amit.reddy@cuanschutz.edu.

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ABSTRACT

Background

Uveitis is a term used to describe a group of intraocular inflammatory diseases. Uveitis is the fifth most common cause of vision loss in high-income countries, with the highest incidence of disease in the working-age population. Corticosteroids are the mainstay of treatment for all subtypes of non-infectious uveitis. They can be administered orally, topically with drops, by periocular (around the eye) or intravitreal (inside the eye) injection, or by surgical implantation.

Objectives

To determine the efficacy and safety of steroid implants in people with chronic non-infectious posterior uveitis, intermediate uveitis, and panuveitis.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register), MEDLINE Ovid, Embase, PubMed, LILACS, and three trials registries to November 2021.

Selection criteria

We included randomized controlled trials comparing either fluocinolone acetonide (FA) or dexamethasone (DEX) intravitreal implants with standard-of-care therapy or sham procedures, with at least six months of follow-up after treatment. We included studies that enrolled participants of all ages, who had chronic non-infectious posterior uveitis, intermediate uveitis, or panuveitis with vision that was better than hand-motion.

Data collection and analysis

We applied standard Cochrane methodology.

Main results

We included data from four trials (683 participants, 907 eyes) that compared corticosteroid implants with either sham or standard-of-care therapy.

Study characteristics and risk of bias

Of the two trials that compared corticosteroid implants with sham procedure, one examined a 0.18 mg FA implant, and the other, a 0.7 mg DEX implant. The other two trials compared a 0.59 mg FA implant with standard-of-care therapy, which included systemic corticosteroids

and immunosuppressive medications, if needed. Considering improvement in visual acuity, we assessed the four trials to be at either low risk, or with some concerns of risk of bias across all domains.

Findings

Using sham procedure as control, combined results at the six-month primary time point suggested that corticosteroid implants may decrease the risk of uveitis recurrence by 60% (relative risk [RR] 0.40, 95% confidence interval [CI] 0.30 to 0.54; 2 trials, 282 participants; low-certainty evidence); and lead to a greater improvement in best-corrected visual acuity (BCVA; mean difference [MD] 0.15 logMAR, 95% CI 0.06 to 0.24; 1 trial, 153 participants; low-certainty evidence). Evidence based on a single-study report (146 participants) suggested that steroid implants may have no effects on visual functioning quality of life, measured on the National Eye Institute 25-Item Visual Function Questionnaire (MD 2.85, 95%CI -3.64 to 9.34; 1 trial, 146 participants; moderate-certainty evidence).

Using standard-of care therapy as control, combined estimates at the 24-month primary time point suggested that corticosteroid implants were likely to decrease the risk of recurrence of uveitis by 54% (RR 0.46, 95% CI 0.35 to 0.60; 2 trials, 619 eyes). Combined estimates at 24 months also suggested that steroid implants may have little to no effects on improving BCVA (MD 0.05 logMAR, 95% CI -0.02 to 0.12; 2 trials, 619 eyes; low-certainty evidence). Evidence based on a single-study report (232 participants) suggested that steroid implants may have minimal clinical effects on visual functioning (MD 4.64, 95% CI 0.13 to 9.15; 1 trial, 232 participants; moderate-certainty evidence); physical functioning (SF-36 physical subscale MD 2.95, 95% CI 0.55 to 5.35; 1 trial, 232 participants; moderate-certainty evidence); or mental health (SF-36 mental subscale MD 3.65, 95% CI 0.52 to 6.78; 1 trial, 232 participants; moderate-certainty evidence); but not on EuroQoL (MD 6.17, 95% CI 1.87 to 10.47; 1 trial, 232 participants; moderate-certainty evidence); or EuroQoL-5D scale (MD 0.02, 95% CI -0.04 to 0.08; 1 trial, 232 participants; moderate-certainty evidence).

Adverse effects

Compared with sham procedures, corticosteroid implants may slightly increase the risk of cataract formation (RR 2.69, 95% CI 1.17 to 6.18; 1 trial, 90 eyes; low-certainty evidence), but not the risk of cataract progression (RR 2.00, 95% CI 0.65 to 6.12; 1 trial, 117 eyes; low-certainty evidence); or the need for surgery (RR 2.98, 95% CI 0.82 to 10.81; 1 trial, 180 eyes; low-certainty evidence), during up to 12 months of follow-up. These implants may increase the risk of elevated intraocular pressure ([IOP] RR 2.81, 95% CI 1.42 to 5.56; 2 trials, 282 participants; moderate-certainty evidence); and the need for IOP-lowering eyedrops (RR 1.85, 95% CI 1.05 to 3.25; 2 trials, 282 participants; moderate-certainty evidence); but not the need for IOP-lowering surgery (RR 0.72, 95% CI 0.13 to 4.17; 2 trials, 282 participants; moderate-certainty evidence).

Evidence comparing the 0.59 mg FA implant with standard-of-care suggested that the implant may increase the risk of cataract progression (RR 2.71, 95% CI 2.06 to 3.56; 2 trials, 210 eyes; low-certainty evidence); and the need for surgery (RR 2.98, 95% CI 2.33 to 3.79; 2 trials, 371 eyes; low-certainty evidence); along with the risk of elevated IOP (RR 3.64, 95% CI 2.71 to 4.87; 2 trials, 605 eyes; moderate-certainty evidence); and the need for medical (RR 3.04, 95% CI 2.36 to 3.91; 2 trials, 544 eyes; moderate-certainty evidence); or surgical interventions (RR 5.43, 95% CI 3.12 to 9.45; 2 trials, 599 eyes; moderate-certainty evidence).

In either comparison, these implants did not increase the risk for endophthalmitis, retinal tear, or retinal detachment (moderate-certainty evidence).

Authors' conclusions

Our confidence is limited that local corticosteroid implants are superior to sham therapy or standard-of-care therapy in reducing the risk of uveitis recurrence. We demonstrated different effectiveness on BCVA relative to comparators in people with non-infectious uveitis. Nevertheless, the evidence suggests that these implants may increase the risk of cataract progression and IOP elevation, which will require interventions over time.

To better understand the efficacy and safety profiles of corticosteroid implants, we need future trials that examine implants of different doses, used for different durations. The trials should measure core standard outcomes that are universally defined, and measured at comparable follow-up time points.

PLAIN LANGUAGE SUMMARY

Steroid implants for chronic uveitis not caused by infection

What is chronic non-infectious uveitis?

Uveitis is a group of eye diseases caused by inflammation (redness, swelling, pain, etc.) inside the eye, which can lead to vision loss. Uveitis can result from infections, or non-infectious causes. Non-infectious uveitis can result from a disease somewhere else in the body. The uvea (middle layer of the eye) has many blood vessels. If the immune system is fighting a problem in one area, the cells and chemicals it makes can travel through the bloodstream and enter the eye, leading to inflammation. Acute uveitis lasts less than three months; chronic uveitis lasts longer than three months.

How it is treated?

Chronic non-infectious uveitis is generally treated with steroids, applied near or inside the eye, or other medicines, taken either by mouth or injection, to control the inflammation. However, these medicines, including steroids, suppress the immune system and result in unwanted side effects.

What did we want to find out?

We assessed whether a steroid-containing implant (a small capsule that slowly releases steroids inside the eye) can reduce the return of uveitis, improve vision, or improve quality of life. We also evaluated whether these implants increased any unwanted side effects.

What we did

We searched for trials that randomly assigned children and adults with chronic non-infectious uveitis to receive either steroid-containing implants or another treatment; the other treatment could be a pretend (sham) procedure or other standard way of delivering care. We summarized the study findings, and assessed how confident we were in the findings.

What we found

We found two studies (282 participants) that compared surgically-placed implants that released fluocinolone acetonide into the eye with a sham procedure. The type and amount of medicine released was different in both studies. The steroid-containing implants appeared to reduce the risk of uveitis coming back, and lead to better vision and quality of life.

We found two studies (683 participants) that compared surgically-placed implants that released fluocinolone acetonide into the eye with standard treatment. Both studies used the same implant. The results did not show that the steroid-containing implants reduced the risk of uveitis coming back, or improved much vision, but the participants appeared to have a better quality of life.

Steroid-containing implants seemed to increase the risk for developing cataracts (clouding of the lens of the eye), and for increasing the pressure in the eye. All four studies included participants from multiple countries.

What are the limitations of the evidence?

We only included four studies. They did not enroll large numbers of participants, and had some flaws in their study design. Therefore, we have moderate to limited confidence in our findings.

How up to date is this evidence?

The evidence is current to November 2021.

Summary of findings 1. Steroid implant versus sham procedure

Steroid implant versus sham procedure for chronic non-infectious uveitis

Patient or population: people with chronic non-infectious uveitis

Settings: eye clinics in North America, Europe, Middle East, and South Asia

Intervention: fluocinolone acetonide 0.18 mg or dexamethasone 0.7 mg implant

Comparison: sham procedure

Outcomes	Illustrative comparative risks (95% CI)		Relative Effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk* with sham procedure	Corresponding risk** with steroid implant				
Proportion of participants with recurrence of uveitis	**Primary time point: 6 months** 57 events per 100 participants	23 events (17 to 31) per 100 persons	**RR 0.40** (0.30 to 0.54)	282 (2)	Low[a,b]	Lower is better
	Secondary time points: ≥ 12 months *12 months*: 98 events per 100 participants *36 months*: 98 events per 100 participants	*12 months*: 38 events (29 to 50) per 100 persons *36 months*: 66 events (56 to 77) per 100 persons	**RR 0.39** (0.30 to 0.51) **RR 0.67** (0.57 to 0.79)	129 (1)		
Mean difference in BCVA (logMAR)	**Primary time point: 6 months** The mean improvement in BCVA in the sham group was 0.07 (SD 0.28)	The mean improvement in BCVA in the steroid implant group was 0.15 higher (0.06 to 0.24)		153 (1)	Low[a,b]	Results are presented as improvement in logMAR, with positive differences indicating more improvement.
	Secondary time points: ≥ 12 months The mean improvement in BCVA in the sham group at *12 months*: 0.07 (SD 0.26) *36 months*: 0.05 (SD 0.28)	The mean improvement in BCVA in the steroid implant group was: *12 months*: 0.05 higher (0.05 lower to 0.15 higher)		129 (1)		

		36 months: 0.13 higher (0.03 to 0.23)				
Mean difference in quality of life scores (NEI-VFQ25)	**Primary time point: 6 months** The mean quality of life scores in the sham group was 73.38 (SD 21.19)	The mean quality of life scores in the steroid implant group was 2.85 higher (3.64 lower to 9.34 higher)		146 (1)	Moderate[b]	MCID was 4 to 6 points (Suner 2009).
Proportion of participants with cataract formation/progression, or surgery	**Cataract formation** 13 events per 100 eyes	34 events (15 to 79) per 100 eyes	**RR 2.69** (1.17 to 6.18)	90 eyes (1)	Low[b,c]	Lower is better. Up to 6 to 12 months post-treatment.
	Cataract progression 7 events per 100 eyes	15 events (5 to 45) per 100 eyes	**RR 2.00** (0.65 to 6.12)	117 eyes (1)		
	Cataract surgery 4 events per 100 eyes	12 events (3 to 43) per 100 eyes	**RR 2.98** (0.82 to 10.81)	180 eyes (1)		
Proportion of participants with elevated IOP or receiving intervention	**Elevated IOP** 8 events per 100 participants	22 events (11 to 44) per 100 participants	**RR 2.81** (1.42 to 5.56)	282 (2)	Moderate[b]	Lower is better. Up to 6 to 12 months post-treatment.
	Requiring medication 9 events per 100 participants	17 events (9 to 29) per 100 participants	**RR 1.85** (1.05 to 3.25)			
	Requiring surgery 20 events per 1000 participants	14 events (3 to 83) per 1000 participants	**RR 0.72** (0.13 to 4.17)			
Proportion of participants with endophthalmitis	17 events per 1000 participants	8 events (2 to 39) per 1000 participants	**RR 0.47** (0.10 to 2.30)	280 (2)	Moderate[b]	Lower is better. Up to 6 to 12 months post-treatment.
Proportion of participants with retinal tear or detachment	17 events per 1000 participants	19 events (4 to 98) per 1000 participants	**RR 1.11** (0.21 to 5.75)	280 (2)	Moderate[b]	Lower is better. Up to 6 to 12 months post-treatment.

*The basis for the **assumed risk** is the mean baseline risk from the studies in the meta-analysis; the total number of events in the control group divided by the total number of participants in the control groups, scaled to 100 or 1000. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**The corresponding risk was the absolute risk (number of events divided by number of participants in the intervention group). The 95% CI was calculated using a binomial distribution.

BCVA: best-corrected visual acuity; **CI:** confidence interval; **DEX:** dexamethasone; **FA:** fluocinolone acetonide; **IOP:** intraocular pressure; **MCID:** minimal clinically important difference; **MD:** mean difference; **No:** number; **NEI-VFQ25:** National Eye Institute 25-Item Visual Function Questionnaire; **RR:** risk ratio

GRADE Working Group grades of evidence
High-certainty. We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate-certainty. We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low-certainty. Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low-certainty. We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded for risk of bias (-1)
[b]Downgraded for imprecision (-1)
[c]Downgraded for indirectness (-1)

Summary of findings 2. Steroid implant versus standard-of-care therapy

Steroid implant versus systemic therapy for chronic non-infectious uveitis

Patient or population: people with chronic non-infectious uveitis

Settings: eye clinics in North America, Europe, Middle East, and Australia

Intervention: fluocinolone acetonide 0.59 mg implant

Comparison: standard-of-care therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of eyes (Studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk* with standard-of-care therapy	Corresponding risk** with steroid implant				
Proportion of eyes with re-currence of uveitis	**Primary time point: 24 months** 38 per 100 eyes	17 events (13 to 23) per 100 eyes	**RR 0.46** (95% CI: 0.35 to 0.60)	619 (2)	Low[a,b]	Lower is better. Combined results were similar at 24 months when using data that excluded inferred recurrence from Pavesio 2010 (RR 0.37,
	Secondary time point: 6 months 43 events per 100 eyes	19 events (15 to 25) per 100 eyes	**RR 0.45** (95% CI: 0.35 to 0.59)			

						95% CI 0.27 to 0.51)
Mean difference in BCVA (logMAR)	**Primary time point: 24 months** The mean improvement in BCVA in the standard-of-care group was 0.04 (SD 0.51)	The mean improvement in BCVA in the steroid implant group was 0.05 higher (0.02 lower to 0.12 higher)	-	619 (2)	Low[a,c]	Results represent improvement in BCVA, with positive differences indicating more improvement. Single-study estimates reported at 6 months by Pavesio 2010 (140 eyes) were similar (MD 0.02, 95% CI -0.08 to 0.12).
	Secondary time point: 12 months The mean improvement in BCVA in the standard-of-care group was 0.06 (SD 0.53)	The mean improvement in BCVA in the steroid implant group was 0.01 higher (0.06 lower to 0.08 higher)	-			
Mean difference in quality of life scores* **	**NEI-VFQ25 composite score** The mean difference in the standard-of-care group was 6.8 (SD 16.87)	The mean difference in the steroid implant group was 4.64 higher (0.13 to 9.15)	-	232 (1)	Moderate[c]	MCID was 4 to 6 points (Suner 2009).
	SF-36 physical The mean difference in the standard-of-care group was -1.8 (SD 9.61)	The mean difference in the steroid implant group was 2.95 higher (0.55 to 5.35)	-			MCID was 3 to 5 points (Hays 2001).
	SF-36 mental The mean difference in the standard-of-care group was -1.1 (SD 12.28)	The mean difference in the steroid implant group was 3.65 higher (0.52 to 6.78)	-			MCID was 3 to 5 points (Hays 2001).
	EuroQoL (VAS) The mean difference in the standard-of-care group was -0.88 (SD 19.01)	The mean difference in the steroid implant group was 6.17 higher (1.87 to 10.47)	-			MCID was 7 points (Pickard 2007).
	EuroQoL-5D The mean difference in the standard-of-care group was 0 (SD 0.21)	The mean difference in the steroid implant group was 0.02 higher (0.04 lower to 0.08 higher)	-			MCID was 0.06 to 0.07 points (Pickard 2007).
Proportion of eyes with cataract for-	**Cataract progression** 33 events per 100 eyes	89 events (68 to 117) per 100 eyes	**RR 2.71** (2.06 to 3.56)	210 (2)	Low[b,c]	Lower is better

mation or progression, or surgery	**Cataract surgery** 27 events per 100 eyes	80 events (63 to 102) per 100 eyes	**RR 2.98** (2.33 to 3.79)	371 (2)		
Proportion of eyes with elevated IOP or receiving intervention	**Elevated IOP** 14 events per 100 eyes	51 events (38 to 68) per 100 eyes	**RR 3.64** (2.71 to 4.87)	605 (2)	Moderate[c]	Lower is better
	Requiring medications 20 events per 100 eyes	61 events (47 to 78) per 100 eyes	**RR 3.04** (2.36 to 3.91)	544 (2)		
	Requiring surgery 5 events per 100 eyes	27 events (16 to 47) per 100 eyes	**RR 5.43** (3.12 to 9.45)	599 (2)		
Proportion of eyes with endophthalmitis****	3 events (0.3 to 22) per 1000 eyes	20 events per 1000 eyes	**RR 7.30** (0.91 to 58.72)	607 (2)	Moderate[c]	Lower is better
Proportion of eyes with retinal tear or detachment	10 events per 1000 eyes	21 events (5 to 84) per 1000 eyes	**RR 2.07** (0.51 to 8.40)	606 (2)	Moderate[c]	Lower is better

*The basis for the **assumed risk** is the mean baseline risk from the studies in the meta-analysis; the total number of events in the control group divided by the total number of participants in the control groups, scaled to 100 or 1000. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**The corresponding risk was the absolute risk (number of events divided by number of participants in the intervention group). The 95% CI was calculated using a binomial distribution.

***A favorable direction of changes differs by questionnaire.

****The corresponding risk is the total number of events in the intervention group divided by the total number of eyes in the intervention groups, scaled to 1000. The assumed risk (and its 95% CI) is based on the assumed risk in the intervention group and the relative effect of the intervention (and its 95% CI).

BCVA: best-corrected visual acuity; **CI:** confidence interval; **FA**, fluocinolone acetonide; **IOP:** intraocular pressure; **MCID:** minimal clinically important difference; **MD:** mean difference; **No:** number; **NEI-VFQ25:** the National Eye Institute 25-Item Visual Function Questionnaire; **RR:** risk ratio; **SD:** standard deviation; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High-certainty. We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate-certainty. We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low-certainty. Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low-certainty. We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded for risk of bias (-1)
[b]Downgraded for indirectness (-1)
[c]Downgraded for imprecision (-1)

BACKGROUND

Description of the condition

Uveitis is a term used to describe a heterogeneous group of intraocular inflammatory diseases of the anterior, intermediate, and posterior uveal tract (iris, ciliary body, choroid). Uveitis is the fifth most common cause of vision loss in high-income countries, accounting for 5% to 20% of legal blindness (Durrani 2004; Nussenblatt 1990), with the highest incidence of disease in the working-age population (Suttorp-Schulten 1996). In low-income countries, uveitis accounts for 2.4% to 24% of legal blindness. Individual estimates are not available for the various causes of infectious uveitis, including onchocerciasis, the fifth-leading cause of blindness worldwide (Durrani 2004; Suttorp-Schulten 1996). A recent, large, retrospective analysis of medical chart records (over a 12-month period) by Gritz and colleagues in California, reported the incidence of uveitis to be 52.4 per 100,000 person-years, which was three times higher than previous estimates (Gritz 2004). Posterior uveitis alone accounts for approximately 15% to 22% of uveitis cases in the United States, and leads to approximately 10% of legal blindness in the United States (Suttorp-Schulten 1996).

Description of the intervention

Corticosteroids are the mainstay acute treatment for all anatomical subtypes of non-infectious uveitis. They can be administered orally, topically with drops or ointments, by periocular (around the eye) or intravitreal (inside the eye) injection, or by surgical implantation (Haupert 2000). Corticosteroids are immunosuppressant medications that reduce inflammation and macular edema (retinal swelling), a principal cause of reduced vision in uveitis. Treatment of posterior uveitis represents a particular therapeutic challenge, because topical steroids rarely reach therapeutic concentrations in the vitreous, thus, people with posterior uveitis often require administration of oral corticosteroids or local steroid injection (Jaffe 2006). These therapeutic modalities may lead to several complications, including cataract formation and elevated intraocular pressure. The systemic morbidity associated with oral steroids includes hyperglycemia (high blood sugar or frank diabetes mellitus), myopathy (muscle damage), secondary infections, impaired wound healing, mental status changes (ranging from mood changes to psychosis), and adrenal suppression (hormone problems). Periocular and intravitreal steroid injections also have limitations: they provide only short-term control, often requiring repeated injections every three to six months to control inflammation, and the injection procedure may be complicated by globe perforation, retinal tears, hemorrhage, endophthalmitis (infection of the eye), ptosis (drooping lid), and fibrosis (Haupert 2000; Jager 2004). In addition to systemic corticosteroids, systemic immunomodulatory therapies, including methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, adalimumab, infliximab, and alkylating agents, such as cyclophosphamide, are used to treat uveitis.

Currently, there is no standardized algorithm for the use of systemic immunosuppressive therapies for non-infectious uveitis, and most specific agents are used off-label for this indication. Many of these therapies can have serious side effects, including increased susceptibility to infection and certain types of cancers, as well as bone marrow suppression (low blood counts, poor blood clotting, decreased ability to fight infection). While these therapies require close monitoring, their long-term side effect profiles may be more favorable than corticosteroids. Except for cyclosporine, which is approved for dry eye syndrome but not commonly used to treat uveitis, none of these therapies are available for local administration to the eye.

How the intervention might work

Several clinical trials have investigated the efficacy of a technology that involves corticosteroid delivery via an intravitreal sustained-release implant (Callanan 2008; Jaffe 2000a; Lowder 2011b; Williams 2009). An intravitreal corticosteroid implant has the theoretical advantage of maintaining an adequate, relatively stable concentration of corticosteroids for several months or years, without repeated intravitreal injection and its inherent risks. Such an implant may decrease or eliminate the need for systemic immune suppression.

The first corticosteroid implant for uveitis to be approved by the U.S. Food and Drug Administration (FDA) was the fluocinolone acetonide (FA) sustained-release implant (Retisert, Bausch & Lomb Inc., Rochester, NY [Callanan 2008; Kempen 2011; Pavesio 2010]). The FDA also approved a short-acting biodegradable dexamethasone intravitreal steroid implant for macular edema caused by retinal vein occlusions and diabetes mellitus, along with non-infectious uveitis affecting the posterior segment (NIPU; Ozurdex, Allergan Inc., Irvine, CA [Haller 2010; Lowder 2011; Taylor 2010]). There is also a non-biodegradable FA implant (Yutiq, Eyepoint Pharmaceuticals Inc., Watertown, MA), which the FDA approved for the treatment of non-infectious posterior uveitis (Jaffe 2019). While such implants may reduce the overall systemic impact of corticosteroids, the increased intraocular exposure may cause higher rates of cataract and glaucoma (Bollinger 2011; Goldstein 2007a; Kempen 2011; Pavesio 2010). These risks must be weighed against their potential benefits.

Why it is important to do this review

This review is needed to enable decision makers (policymakers, clinicians, and people with uveitis) to weigh the benefits and risks of steroid implants when choosing the best option for the treatment of uveitis. These implants are expensive; in 2006, the 0.59 mg FA implant (Retisert) cost approximately USD 20,000, the 0.18 mg FA implant cost USD 10,000, and the dexamethasone 0.7-mg dexamethasoneimplant cost USD 1500 (Mohammad 2007).

OBJECTIVES

To determine the efficacy and safety of steroid implants in people with chronic non-infectious posterior uveitis, intermediate uveitis, and panuveitis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) that compared a corticosteroid implant with a sham procedure or standard-of-care therapy.

Types of participants

We included studies that enrolled participants with better than hand-motion vision and a history of chronic posterior uveitis,

intermediate uveitis, or panuveitis (one eye with a history of recurrent non-infectious uveitis affecting the posterior segment), who required systemic corticosteroids for more than one month, or multiple sub-Tenon's capsule corticosteroid injections. We included studies with both active and quiescent disease.

We excluded studies that enrolled participants with infectious uveitis.

The review protocol initially planned to only include studies that enrolled participants 18 years of age or older (Brady 2013). Authors of the previous version eliminated the age restriction (Brady 2016); which we continued for the current update.

Types of interventions

We included trials comparing fluocinolone acetonide or dexamethasone intravitreous implants with standard-of-care therapy (for example systemic steroids, intravitreal steroids, disease-modifying antirheumatic drugs), or sham injection. For trials that tested against standard-of-care therapy, the implants were used alongside traditional topical or systemic anti-inflammatory therapies, as long as the dosage was stable at the time of enrollment, reflecting the fact that these medications are used both as monotherapy and add-on therapy.

Types of outcome measures

Critical outcome

The critical outcome was the proportion of participants (or eyes) with a recurrence of uveitis at six months, or at the primary efficacy time point defined by the included trial. The definition of recurrence included any of the following:

- Increase in vitreous haze by two or more steps above baseline;
- Increase in anterior chamber cell by two or more steps above baseline;
- Clinical indication to add or increase dose of systemic anti-inflammatory medication to control inflammation.

Important outcomes

Important outcomes assessed at six months, or at the primary efficacy time point of the trial, included:

- Mean difference in best-corrected distance visual acuity (BCVA), measured by the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart, Snellen chart, or Snellen equivalent;
- Mean difference in quality of life (QoL) scores, measured by any validated measures presented, e.g. National Eye Institute Visual Functioning Questionnaire (NEI-VFQ), 36-Item Short Form Health Survey (SF-36);
- Adverse events: we assessed the proportion of participants (or eyes) who experienced the following conditions through to the end of the trial period:
  - Cataract formation or progression, or participants with phakic eyes that required cataract extraction surgery;
  - Elevated intraocular pressure (IOP) > 10 mmHg over baseline, or receiving intervention (eye drops or surgery);
  - Endophthalmitis;
  - Retinal tear or retinal detachment;
  - Systemic adverse events related to steroid or immunomodulatory therapy.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; which contains the Cochrane Eyes and Vision Trials Register; 2021, Issue 11) in the Cochrane Library (searched 16 November 2021; Appendix 1), MEDLINE Ovid, MEDLINE Ovid In-Process and Other Non-Indexed Citations, MEDLINE Ovid Daily, OLDMEDLINE Ovid (January 1946 to 16 November 2021; Appendix 2), PubMed (1948 to 16 November 2021; Appendix 3), Embase (January 1980 to 16 November 2021; Appendix 4), Latin American and Caribbean Health Sciences Literature Database (LILACS; 1982 to 16 November 2021; Appendix 5), the *meta*Register of Controlled Trials (*m*RCT; searched 16 November 2021; Appendix 6), ClinicalTrials.gov (www.clinicaltrials.gov; searched 16 November 2021; Appendix 7), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/search/en; searched 16 November 2021; Appendix 8). We did not use any date or language restrictions in the electronic search for studies.

Searching other resources

We searched the reference lists of included studies, review articles, and guidelines to identify additional studies. We did not search meeting abstracts for the American Academy of Ophthalmology, the American Academy of Optometry, or the Association for Research in Vision and Ophthalmology, because these conference proceedings are included in CENTRAL.

Data collection and analysis

Selection of studies

Review authors worked in pairs to independently review the titles and abstracts of all records identified through the electronic searches, using the web-based review management software Covidence. For studies that appeared to meet the inclusion criteria, or for which the information provided in the title and abstract were insufficient for us to make a clear decision, we obtained the full-text reports. Two review authors independently assessed the full-text reports to determine whether the studies met the inclusion criteria. We resolved any disagreement at either stage of screening by discussion. All publications from studies meeting the inclusion criteria underwent an assessment of risk of bias and data extraction. We recorded studies that were excluded after screening the full-text report or subsequent stages of the review process in the Characteristics of excluded studies table, with reasons for exclusion documented.

Data extraction and management

Two review authors independently extracted the data for study design, participant characteristics, and the critical and important outcomes onto electronic data collection forms, developed by Cochrane Eyes and Vision in Covidence. We resolved discrepancies by discussion. We also contacted the trial investigator or corresponding author of eligible trials to request additional information if the reporting of methods or results was unclear. If the investigator or author did not reply within two weeks, we extracted the relevant information available to us from trial registers or published full-text reports.

For each included study, we put the following characteristics into RevMan Web 2022: year of publication, country from which participants were recruited, and source of study funding; details of the participants, including demographic characteristics and inclusion criteria; details of the type of intervention; details of the outcomes reported, including adverse events, and the method of assessment and time intervals. We extracted continuous variables as means, standard deviations, or the associated 95% confidence intervals (CI); dichotomous variables as number of participants (or eyes) for which the outcome was measured. Specifically, for changes in BCVA that were measured in ETDRS letters, we converted letters into logMAR units before meta-analysis (Ferris 1982). In some studies, we were only able to extract numerical data from figures, by applying a free, web-based software suggested in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Li 2021; WebPlotDigitizer 2021).

Assessment of risk of bias in included studies

For the current update, we applied Cochrane's RoB 2 tool for risk assessment (Higgins 2021). Two review authors independently assessed the risk of bias for two outcomes: recurrence of uveitis and BCVA. We resolved disagreements on the RoB assessment by discussion within the author team.

We examined and reported on five domains.

1. Bias arising from the randomization process
2. Bias introduced by deviations from intended interventions
3. Bias due to missing outcome data
4. Bias in outcome measurement
5. Bias in selective reporting of outcome data

For each outcome specified for risk of bias assessment, we judged each domain as having low, high, or some concerns about risk of bias in accordance with signaling questions, for each included study that reported the outcome. At the study level, we provided an overall assessment on the risk of bias as:

1. Low, if we judged all domains to be at low risk of bias;
2. Some concerns, if we judged one or more domains to have some concerns, and none were at high risk;
3. High, if we judged one or more domains at high risk, or if we judged multiple domains to have some concerns (Higgins 2021).

Measures of treatment effect

For continuous outcomes (visual acuity and quality of life scores), we calculated mean differences (MD) with 95% CIs. For dichotomous outcomes, we calculated risk ratios (RR) with 95% CIs for proportions of participants (or eyes) with recurrence of uveitis. For prespecified adverse events, we reported RRs for proportion of eyes, to accommodate eye-level data reported by Kempen 2011; the other three trials included only one study eye per participant.

Unit of analysis issues

The unit of analysis was a single eye for the majority of outcomes: recurrence rate of posterior uveitis, intermediate uveitis, or panuveitis; visual acuity; elevated intraocular pressure requiring intervention; reduction of cystoid macular edema; need for additional therapeutic modalities to control inflammation; cataract formation; cataract extraction; endophthalmitis; retinal tear, or retinal detachment.

The unit of analysis was the person for quality of life outcomes and potential systemic complications of therapy.

Dealing with missing data

We used imputed data reported and described by the trial investigators in the full-text reports; we did not impute missing data ourselves. We contacted trial investigators for missing data. Since trial investigators did not respond (Pavesio 2010), or were unable to provide additional data (Kempen 2011), we extracted data available from the published report. For outcomes for which point estimates of the two comparison groups and P values were reported, we derived the between-group standard deviation assuming Student t distribution, as suggested in Chapter 6 of the *Cochrane Handbook* (Li 2021).

Assessment of heterogeneity

We assessed the included trials for both clinical and methodological diversity by examining characteristics of the trial design, eligibility of trial participants, intervention and comparator differences, and outcome definitions. We assessed statistical heterogeneity using the I^2 statistic, and considered the following thresholds when interpreting I^2 values (Deeks 2021):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We assessed selective outcome reporting by comparing the outcomes specified in the study protocol or the methods section of the study report with the data reported in the study results, as guided by relevant signaling questions in the RoB 2 tool (Higgins 2021).

Data synthesis

We synthesized data from the included trials both qualitatively and quantitatively, according to the guidelines in Chapter 10 of the *Cochrane Handbook* (Deeks 2021). We calculated a summary risk ratio for dichotomous outcomes, and a summary mean difference for continuous outcomes, using random-effects models if there were three or more trials reporting on the same outcome; otherwise, we used fixed-effects models. When there was evidence of considerable clinical, methodological, or statistical heterogeneity across trials, we did not combine the data but described them qualitatively.

Subgroup analysis and investigation of heterogeneity

We did not conduct subgroup analyses because of the small number of included studies and methodologic heterogeneity.

Sensitivity analysis

We did not perform sensitivity analysis by age or clinical heterogeneity as planned in the protocol because of the small number of included trials (Brady 2013).

Summary of findings and assessment of the certainty of the evidence

We developed summary of findings tables, which included the assumed risk and corresponding risk for the following outcomes, based on the risk across control groups in the included studies:

1. Proportion of participants (or eyes) with recurrence of uveitis
2. Mean difference in BCVA
3. Mean difference in quality of life scores
4. Proportion of participants (or eyes) with cataract formation/ progression or surgery
5. Proportion of participants (or eyes) with elevated IOP > 10 mmHg over baseline or receiving intervention
6. Proportion of participants (or eyes) with endophthalmitis
7. Proportion of participants (or eyes) with retinal tear or retinal detachment

We graded the overall certainty of the evidence for each outcome using the GRADE classification (Schünemann 2013). We assessed the certainty of evidence for each outcome as high, moderate, low, or very low, according to (1) high risk of bias; (2) indirectness of evidence; (3) unexplained heterogeneity or inconsistency of results; (4) imprecision; (5) high probability of publication bias, as described in Chapter 14 of the *Cochrane Handbook* (Schünemann 2021).

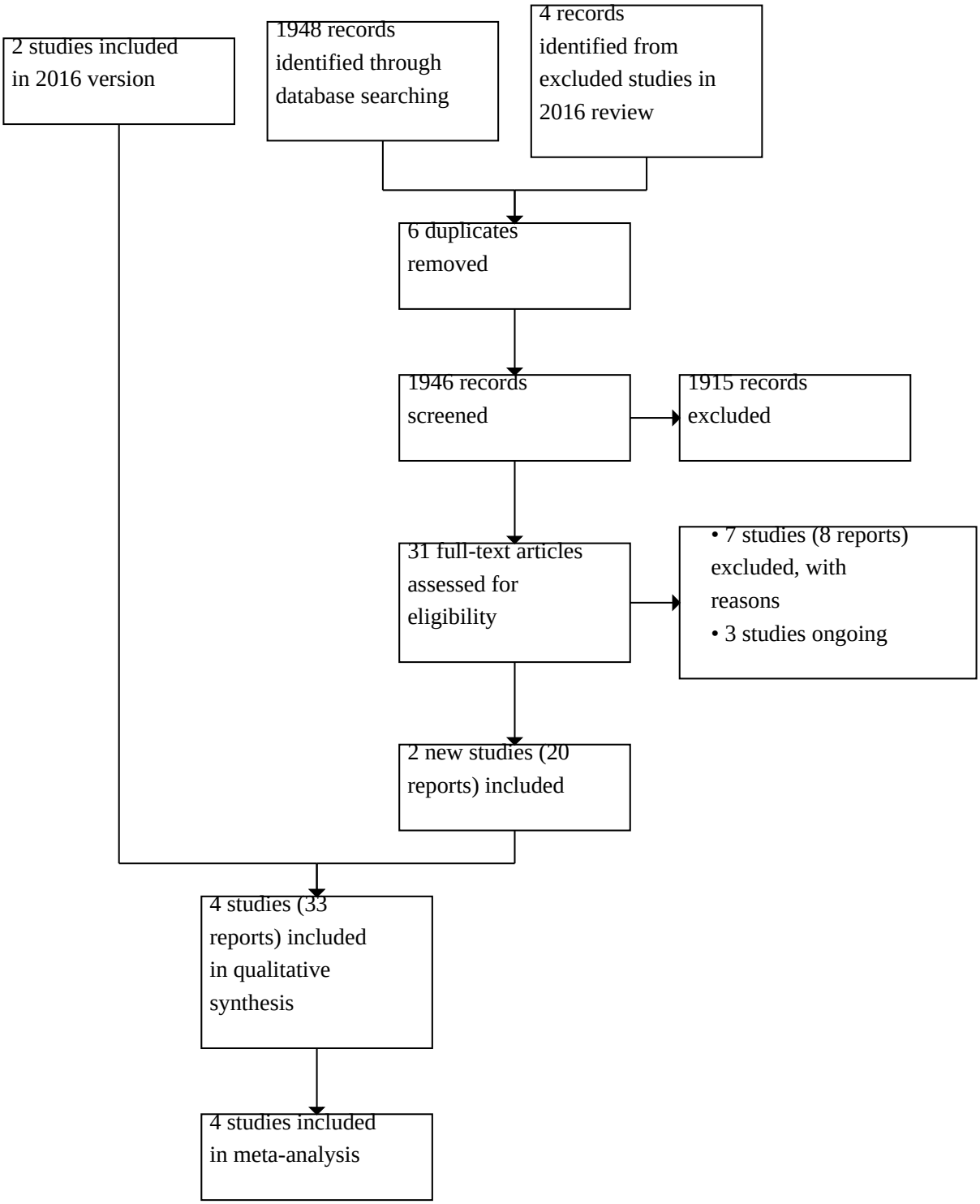
RESULTS

Description of studies

Results of the search

In the 2016 version of the review, the review authors screened 2741 records, excluded 46 full-text reports, and included two studies (Kempen 2011; Pavesio 2010). While updating the literature search in November 2021, we identified 1952 titles and abstracts, four of which we found by screening the Characteristics of excluded studies in the 2016 review. Overall, we screened 31 full-text records for eligibility. We excluded seven studies (eight reports) with reasons, listed in the Characteristics of excluded studies table; three studies were ongoing trials, and we included two new trials (20 reports) in the current review (Jaffe 2019; Lowder 2011). See Figure 1. In total, we included four trials for evidence synthesis in this review. We described the individual included trials in the Characteristics of included studies table.

Figure 1. Flow diagram for study selection for the 2022 update



Included studies

Types of studies

All four included studies were randomized controlled trials (RCTs) with a parallel-group design, conducted among participants with a diagnosis of chronic non-infectious uveitis affecting the posterior segment. Each participant was assigned randomly to the intervention or comparator group in all trials. Two trials randomized participants to either intraocular corticosteroid implant or standard-of-care systemic therapy (Kempen 2011; Pavesio 2010), while the other two trials randomized participants to either intraocular corticosteroid implant or sham procedure (Jaffe 2019; Lowder 2011).

Three of the four trials had two study arms. Lowder 2011 had three study arms (0.7 mg dexamethasone [DEX] implant, 0.35 mg DEX implant, and sham injection), however, we did not include data from the 0.35 mg DEX implant arm in our analysis, as this implant has never been commercially available. The included trials were all multicenter, international trials. Studies were published between 2010 and 2019. All studies reported industry funding or free intervention implants from the industry (Kempen 2011), and all trials reported information on trial registration with publicly available study protocols.

Types of participants

The four trials enrolled a total of 683 participants (907 eyes), with 129 to 240 participants enrolled per study. The percentage of female participants ranged from 48.5% to 71%; the age of participants (when reported) ranged from 12 to 74 years. All included trials enrolled participants with a clinically similar diagnosis of non-infectious posterior uveitis, but with slightly different study populations: Pavesio 2010 enrolled participants who had clinically quiet non-infectious posterior uveitis, while the other three trials enrolled participants who had active non-infectious posterior uveitis in the study eye at the time of randomization (Jaffe 2019; Kempen 2011; Lowder 2011).

For participants with unilateral disease, the affected eye was the study eye. However, each study handled participants with bilateral disease differently. Pavesio 2010 chose the more severely affected eye as the study eye; Lowder 2011 treated the right eye as the study eye; Jaffe 2019 used the more severely affected eye in asymmetric bilateral disease, and the right eye in symmetric bilateral disease as the study eye; Kempen 2011 treated both eyes as study eyes in bilateral disease.

Types of interventions

Pavesio 2010 and Kempen 2011 used 0.59 mg fluocinolone acetonide (FA) intravitreal implant for their intervention group. These two trials used comparable standard-of-care systemic therapy comparison groups. The 0.59 mg FA implant could slowly release medication for approximately 30 months. Lowder 2011 used the 0.7 mg DEX implant for their intervention group, which would release medication for approximately three months. Jaffe 2019 used the 0.18 mg FA intravitreal implant for their intervention group, which could release medication for approximately 36 months.

Participants in the standard-of-care systemic therapy groups in Pavesio 2010 and Kempen 2011 were initially treated with oral corticosteroids, to which systemic immunomodulatory therapy was added if the uveitis recurred during tapering of corticosteroids. Both Lowder 2011 and Jaffe 2019 used similar procedures for participants in the sham procedure group, during which a blunt needle was applied against the sclera to mimic the injection procedure, thereby masking the participant.

We stratified the analysis by control treatment. Comparison 1 (corticosteroid implant versus sham) included data from Lowder 2011 and Jaffe 2019. Comparison 2 (corticosteroid implant versus standard-of-care systemic therapy) included data from Pavesio 2010 and Kempen 2011.

Types of outcomes

Critical outcomes

Recurrence of uveitis

Lowder 2011 and Jaffe 2019 both reported on this critical outcome at six months. Jaffe 2019 also reported on this outcome at 12 and 36 months post-treatment. Pavesio 2010 reported only at 12 and 24 months post-treatment. Kempen 2011 did not report on the recurrence of uveitis, but rather the proportion of eyes with 'residual active uveitis' at each study visit, and the percentage of eyes with control of uveitis at 24-month follow-up, which was also included in our analysis as a surrogate indicator for recurrence of uveitis.

Uveitis recurrence and activity were defined by clinical parameters (anterior chamber cells, vitreous haze, or decrease in visual acuity, or a combination) by Pavesio 2010, Kempen 2011, and Jaffe 2019. For Lowder 2011, we inferred data on recurrence of uveitis from 'the need for anti-inflammatory rescue medication', reported by the authors.

Important outcomes

Mean difference in BCVA

Lowder 2011 reported change in BCVA from baseline at 6 months, Jaffe 2019 reported this at 12 months, and Kempen 2011 at 12 and 24 months. Pavesio 2010 reported the mean change in BCVA at each visit through to 24 months, along with the proportion of participants with improved visual acuity (defined as more than 15 letters on ETDRS chart from baseline).

Mean difference in QoL scores

Both Kempen 2011 and Lowder 2011 (via a sub-analysis paper, Lightman 2013) reported on quality of life outcomes. Kempen 2011 used three different instruments to measure quality of life: the NEI-VFQ, the SF-36, and the EuroQoL questionnaire (EuroQol 1990). The EuroQoL questionnaire included a visual analogue scale (VAS) for overall health-related quality of life, and an EQ-5D health utility index (Kempen 2011). Data were presented as mean changes from baseline to 12 months and 24 months, which we included in our analysis. Lightman 2013 also used the NEI-VFQ, presenting data at 8 weeks, 16 weeks, and 26 weeks. We included data from this paper at six months.

Adverse events

Proportion of participants (or eyes) with cataract formation or progression, or participants with phakic eyes who required cataract extraction surgery

Two of the four trials reported the number of phakic eyes with cataract progression (Lowder 2011; Pavesio 2010); the other two

reported on the incidence of cataract formation in initially non-phakic eyes (Kempen 2011; Jaffe 2019). All four trials reported the number of phakic eyes that required cataract extraction after the intervention.

- ***Cataract progression***: Pavesio 2010 reported a total of 106 phakic eyes in their study, and defined cataract progression as a change of two grades or more in lens opacity. Kempen 2011 reported the number of phakic eyes that underwent surgery by group, during the 24-month study period. Lowder 2011 reported a total of 117 phakic eyes; 47 of which had cataracts at the time of enrollment; formation and progression of cataracts were identified by biomicroscopy evaluation. Jaffe 2019 reported a total of 63 phakic eyes and the number of eyes that underwent cataract extraction surgeries during the first 12 months of the study.
- ***Cataract formation***: Kempen 2011 defined cataract formation as the identification of cataract by biomicroscopy evaluation at two consecutive visits, and reported incident cataract formation in 54 at-risk eyes. In a post-hoc analysis, Jaffe 2019 also compared risks for cataract formation among 90 study (at-risk) eyes.

Proportion of participants (or eyes) with elevated intraocular pressure (IOP) > 10 mmHg over baseline or receiving intervention (eye drops or surgery)

All four trials reported on either or both outcomes, but used different threshold values for IOP elevation. Pavesio 2010 reported on IOP elevation of 10 mmHg or more from baseline; Kempen 2011 reported on IOP elevation of 10 mmHg or more from baseline and an absolute IOP of 30 mmHg or more; Lowder 2011 reported absolute IOP of 25 mmHg or more, and 35 mmHg or more; Jaffe 2019 reported on mean IOP and mean IOP change from baseline, along with IOP elevation of 12 mmHg or more from baseline, and absolute IOP higher than 25 mmHg and 30 mmHg.

Proportion of participants (or eyes) with endophthalmitis

All four trials measured infectious endophthalmitis clinically, by a biomicroscopy examination at each study visit.

Proportion of participants (or eyes) with retinal tear or retinal detachment

All four trials evaluated retinal tear and retinal detachment clinically, by biomicroscopy and indirect ophthalmoscopy examination during the trial period.

Proportion of participants with systemic adverse events related to steroid or immunomodulatory therapy

Only one trial reported systemic adverse events that could be considered to be related to steroid therapy, up to 24 months after treatment, such as hyperlipidemia diagnosis requiring treatment, hypertension diagnosis requiring treatment, diabetes mellitus, osteoporosis, white blood cell count less than 2500/mL, elevated liver enzymes, cancer diagnosis, and death (Kempen 2011).

Excluded studies

After the full-text assessment, we excluded seven studies (eight reports; see Characteristics of excluded studies): three were non-RCTs or dose-response trials (Ciulla 2021; Cornish 2018; Errera 2019); two enrolled non-uveitis participants (Couret 2020; NCT04976777); one compared different implant applicators (NCT02748512); Callanan 2020 was withdrawn from publication.

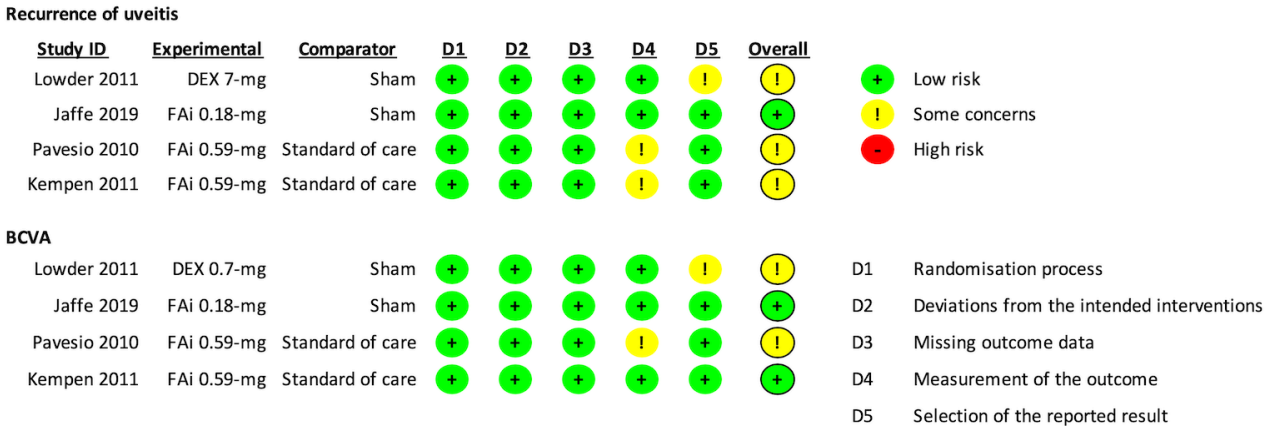
We identified three new ongoing studies (ChiCTR1900026160; NCT05070728; NCT05101928). We have no trials awaiting classification.

Risk of bias in included studies

We assessed the risk of bias using the RoB 2 tool for two outcomes we specified before data extraction, recurrence of uveitis and mean improvement in BCVA. Three of the four trials reported on both outcomes; Kempen 2011 did not specify recurrence of uveitis as a trial outcome, but reported the proportion of eyes with residual active uveitis at each study visit. As this outcome also evaluated control of inflammation, albeit in a broader manner, we included Kempen 2011 in our risk of bias assessment for recurrence of uveitis.

For recurrence of uveitis, we judged only one trial to be at low risk (25%) across all domains assessed; we had some concerns that the other three trials might have some bias due to biased outcome measurement or selective reporting (Figure 2). For mean improvement in BCVA, we considered two trials at low risk (50%) in all domains, whereas we had some concerns for the other two, in either biased outcome measurement or reporting (Figure 2).

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias domain for each trial that reported recurrence of uveitis and BCVA



Bias arising from the randomization process

We judged all four trials at low risk of bias arising from the randomization process for both uveitis recurrence and visual acuity outcomes.

Bias due to deviations from the intended intervention

We judged all four trials at low risk of bias in this domain for both uveitis recurrence and visual acuity outcomes.

Bias due to missing outcome data

We judged all four trials at low risk of bias for missing outcome data for both uveitis recurrence and visual acuity outcomes.

Bias in measurement of the outcome

We judged two of the four trials at low risk of measurement bias for both uveitis recurrence and visual acuity outcomes (Jaffe 2019; Lowder 2011).

We had some concerns of risk of measurement bias of uveitis recurrence, as not all investigators were masked to the treatment received by participants in two trials (Kempen 2011; Pavesio 2010). We judged that Kempen 2011 was at low risk of bias for visual acuity, but we had some concerns for Pavesio 2010's measurement of visual acuity, as it was unclear whether participants and assessors were masked during BCVA measurements.

Bias in selection of the reported result

We judged three of the four included trials at low risk of bias in this domain for both uveitis recurrence and visual acuity (Jaffe 2019; Kempen 2011; Pavesio 2010). We had some concerns for Lowder 2011's measurement of both uveitis recurrence and visual acuity, as there was neither a study protocol nor an analytic plan for the evaluation of potential risks.

Effects of interventions

See: **Summary of findings 1** Steroid implant versus sham procedure; **Summary of findings 2** Steroid implant versus standard-of-care therapy

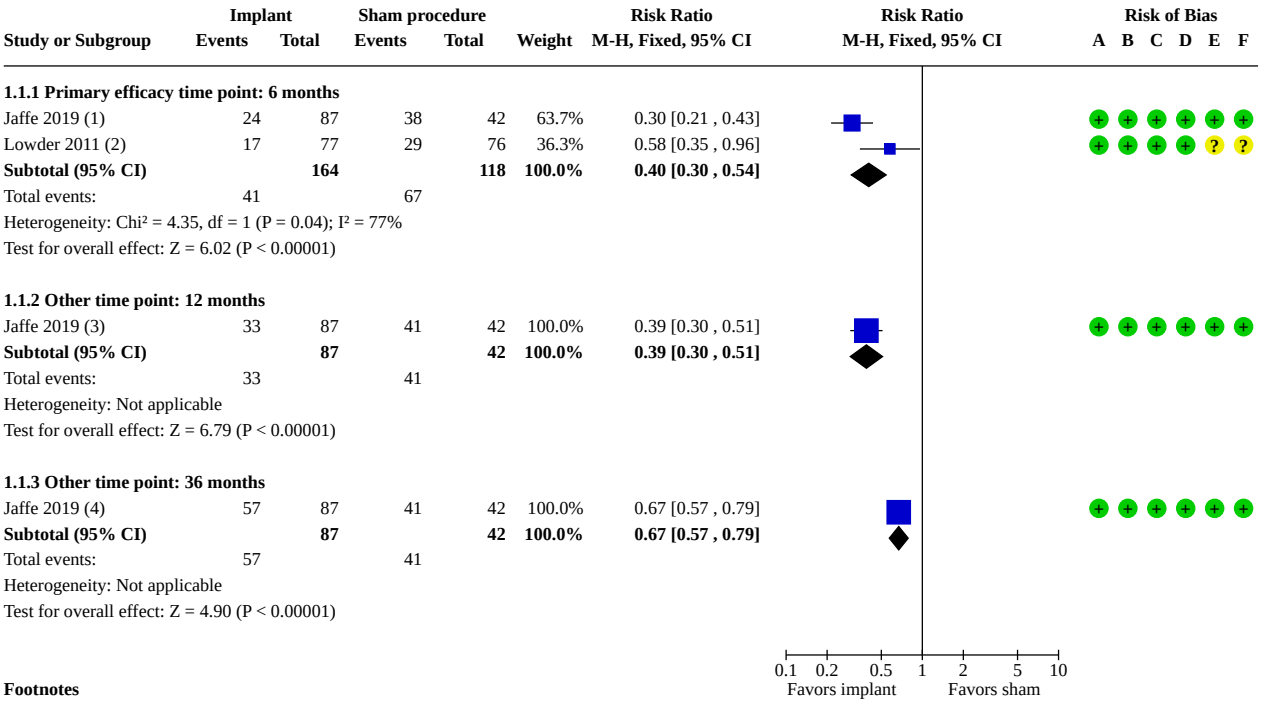
Comparison 1. Corticosteroid implant versus sham procedure

Critical outcome

Proportion of participants (or eyes) with recurrence of uveitis

Both Lowder 2011 and Jaffe 2019 evaluated the proportion of participants who had a recurrence of uveitis at six months, when comparing those who received a corticosteroid implant with those who underwent a sham procedure. Lowder 2011 used a short-acting (three-month) corticosteroid implant, while Jaffe 2019 used a long-acting (36-month) implant. Combined results at the six-month primary time point suggested that corticosteroid implants may decrease the risk of uveitis recurrence by 60% (risk ratio [RR] 0.40, 95% confidence interval [CI] 0.30 to 0.54; P = 0.04, I^2 = 77%; 2 trials, 282 participants; Analysis 1.1; Figure 3; low-certainty evidence) when compared with sham injection. Results were similar for the secondary time points, at 12 and 36 months, according to a single-study estimate from Jaffe 2019 (Analysis 1.1). We downgraded the certainty of evidence for risk of bias (-1) and imprecision (-1).

Figure 3. Forest plot of comparison 1: Steroid implant versus sham procedure, outcome: 1.1 Proportion of participants with recurrence of uveitis.



Footnotes

(1) FAi 0.18 mg, at 6 months
(2) DEX 0.4 mg, at 26 weeks
(3) FAi 0.18 mg, at 12 months
(4) FAi 0.18 mg, at 36 months

Risk of bias legend

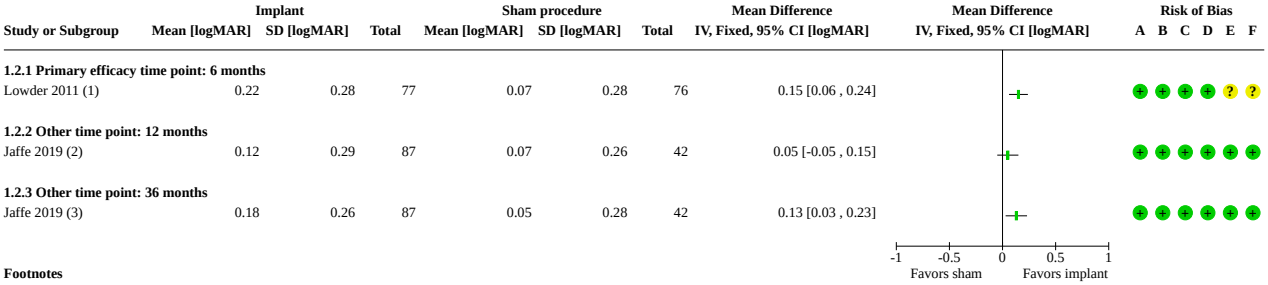
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Important outcomes

Mean difference in BCVA

For the six-month primary time point, a single-study estimate from Lowder 2011 suggested that corticosteroid implants may lead to a greater improvement in BCVA ([mean difference] MD 0.15 logMAR, 95% CI 0.06 to 0.24; 1 trial, 153 participants; Analysis 1.2; low-certainty evidence) than a sham injection. Results were comparable for the secondary time points of 12 and 36 months, according to the single-study estimates from Jaffe 2019 (Analysis 1.2; Figure 4). We downgraded the certainty of the evidence for risk of bias (-1) and imprecision (-1).

Figure 4. Forest plot of comparison 1: Steroid implant versus sham procedure, outcome: 1.2 Improvement in BCVA in logMAR.



Footnotes
(1) DEX 0.7 mg, at 6 months
(2) FAi 0.18 mg, at 12 months
(3) FAi 0.18 mg, at 36 months

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Mean difference in quality of life scores

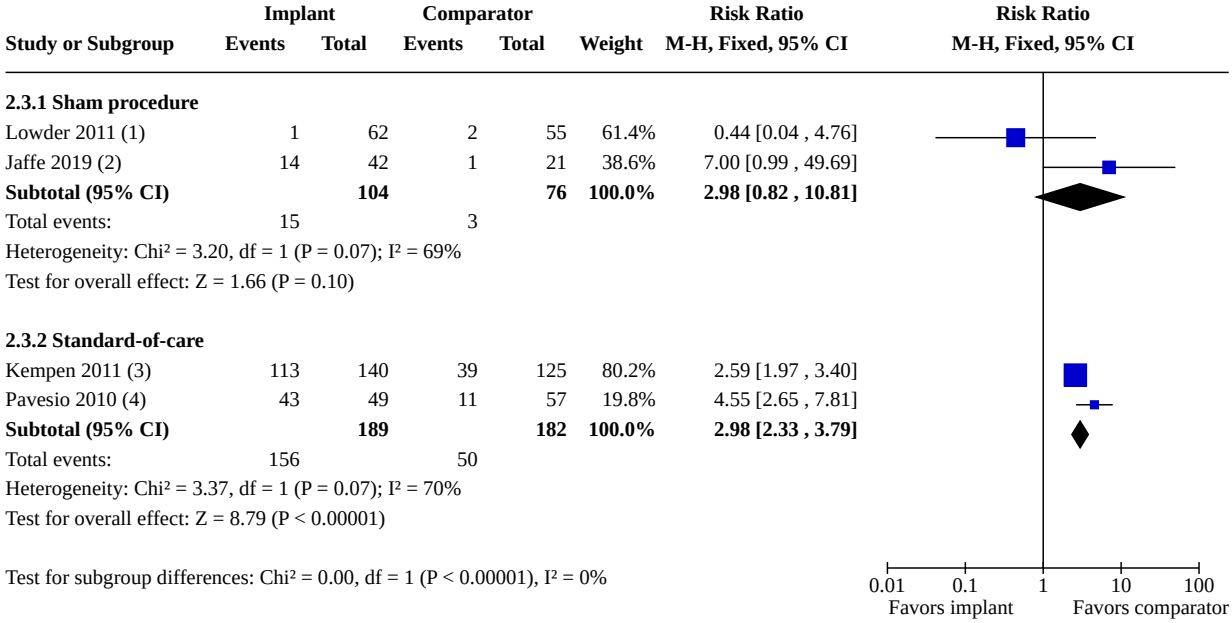
Only one study reported on quality of life scores (Lowder 2011, via a sub-analysis in Lightman 2013). They used the NEI-VFQ questionnaire to assess changes in participant-reported quality of life over the study period, with a suggested minimal clinically important difference (MCID) of four to six points (Suner 2009). The single-study estimates suggested that the corticosteroid implants resulted in little or no differences in the NEI-VFQ scores (MD 2.85, 95% CI -3.64 to 9.34; 1 trial, 146 participants; Analysis 1.3; moderate-certainty evidence) compared with sham injection. We downgraded the certainty of the evidence for imprecision (-1).

Adverse events

Proportion of participants (or eyes) with cataract formation, progression, or participants with phakic eyes who required cataract extraction surgery

- ***Cataract formation***: Jaffe 2019 reported on the implant-associated risk of new cataract formation in 90 initially aphakic eyes. The single-study estimates suggested that a corticosteroid implant may increase the risk of cataract formation compared with a sham procedure (RR 2.69, 95% CI:1.17 to 6.18; 1 trial, 90 eyes; Analysis 2.1; low-certainty evidence).
- ***Cataract progression***: Lowder 2011 reported the risk of cataract progression in 117 phakic eyes, and suggested that corticosteroid implants may not increase cataract progression (RR 2.00, 95% CI 0.65 to 6.12; 1 trial, 117 eyes; Analysis 2.2; low-certainty evidence) when compared with sham injection. This finding was comparable to the combined estimates for risks of 180 phakic eyes that underwent cataract extraction surgery during the trial period (RR 2.98, 95% CI: 0.82 to 10.81; 2 trials, 180 eyes; Analysis 2.3; low-certainty evidence; Figure 5).

Figure 5. Forest plot of comparisons 1 and 3, outcome: 2.3 Proportion of participants or eyes that underwent cataract surgery. Trials in comparison 1 and Pavesio 2010 in comparison 3 included one study eye per participant; Kempen 2011 in comparison 3 reported eye-level outcome data.



Footnotes

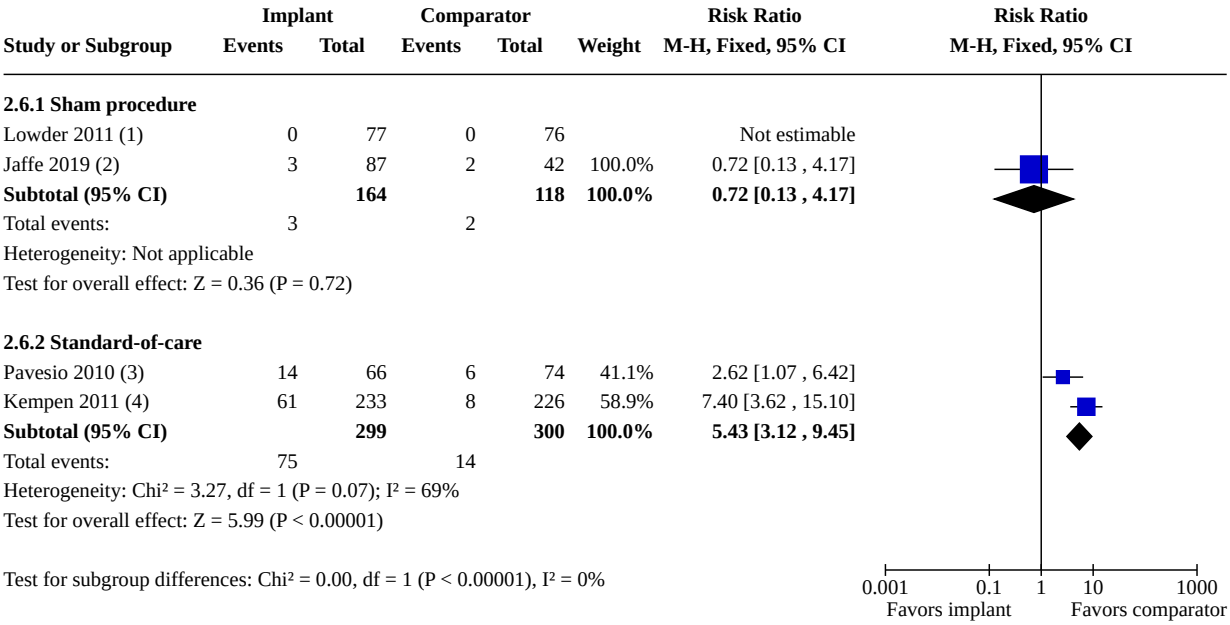
(1) DEX 0.7 mg, at 26 weeks, denominators were phakic eyes at baseline
(2) FAi 0.18 mg, at 12 months, denominators were phakic eyes at baseline
(3) FAi 0.59 mg, at 24 months, denominators were 'at-risk' eyes at baseline
(4) FAi 0.59 mg, at 24 months, denominators were phakic eyes at baseline

We downgraded the certainty of the evidence for indirectness (-1) and imprecision (-1).

Proportion of participants (or eyes) with elevated intraocular pressure (IOP) > 10 mmHg over baseline or receiving intervention (eye drops or surgery)

- ***Elevated IOP***: combined results suggested a corticosteroid implant may increase the risk of elevated IOP by 2.81 times of that in the sham group (95% CI 1.42 to 5.56; 2 trials, 282 participants; Analysis 2.4; moderate-certainty evidence).
- ***Elevated IOP requiring intervention:*** when compared with sham injection, steroid implants may increase the risk of requiring IOP-lowering topical medication by 1.85 times (95% CI 1.05 to 3.25; 2 trials, 282 participants; Analysis 2.5; moderate-certainty evidence). However, steroid implants likely resulted in comparable risks of elevated IOP that required IOP-lowering surgery between the two comparison groups (RR 0.72, 95% CI 0.13 to 4.17; 2 trials, 282 participants; Analysis 2.6; moderate-certainty evidence; Figure 6).

Figure 6. Forest plot of comparisons 1 and 3, outcome: 2.6 Proportion of participants or eyes that underwent IOP-lowering surgery. Trials in comparison 1 and Pavesio 2010 in comparison 3 included one study eye per participant; Kempen 2011 in comparison 3 reported eye-level outcome data.



Footnotes
(1) DEX 0.7 mg, at 26 weeks
(2) FAi 0.18 mg, at 12 months
(3) FAi 0.59 mg, at 24 months
(4) FAi 0.59 mg, at 24 months, eye was unit of analysis

We downgraded the certainty of the evidence for imprecision (-1).

Proportion of participants (or eyes) with endophthalmitis

Combined results suggested that steroid implants probably do not increase the risk of endophthalmitis over the sham procedure (RR 0.47, 95% CI 0.10 to 2.30; 2 trials; 280 participants; Analysis 2.7; moderate-certainty evidence). We downgraded the certainty of the evidence for imprecision (-1).

Proportion of participants (or eyes) with retinal tear or retinal detachment

Combined results suggested that corticosteroid implants likely do not increase the risk of retinal tear or retinal detachment over the sham procedure (RR 1.11, 95% CI 0.21 to 5.75; 2 trials, 280 participants; Analysis 2.8; moderate-certainty evidence). We downgraded the certainty of the evidence for imprecision (-1).

Proportion of participants with systemic adverse events related to steroid or immunomodulatory therapy

Neither trial provided usable data for this outcome. Lowder 2011 reported that "there were no notable changes from baseline in any vital signs or physical findings"; Jaffe 2019 reported that "approximately half of the participants in both treatment groups experienced a non-ocular adverse event during the first 12 months of study", yet the study authors did not specify whether, or how many of these events were related to steroid or immunotherapy.

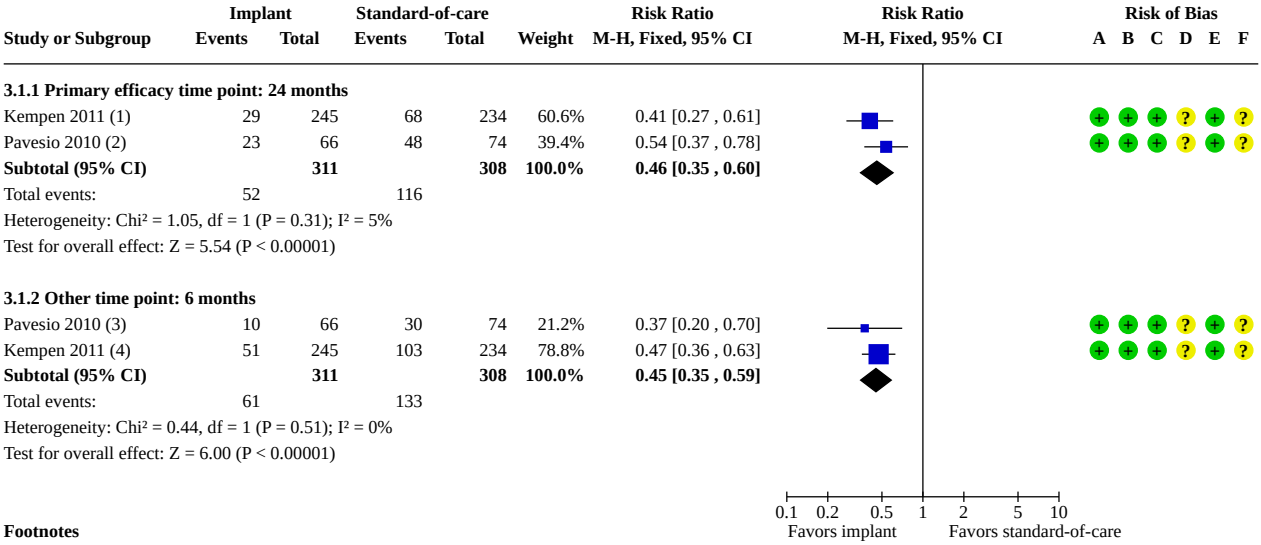
Comparison 2. Corticosteroid implant versus standard-of-care therapy

Critical outcomes

Proportion of participants (or eyes) with recurrence of uveitis

Pavesio 2010 evaluated the proportion of participants who had a recurrence of uveitis at 6 and 24 months, comparing those who received a corticosteroid implant with those who received standard-of-care systemic therapy, whereas Kempen 2011 evaluated the proportion of participants who had residual uveitis activity. Both trials used a long-acting (30-month) implant. Based on combined estimates at the 24-month primary time point, corticosteroid implants were likely to decrease the risk of recurrence of uveitis by 54% (RR 0.46, 95% CI 0.35 to 0.60; 2 trials, 619 eyes; Analysis 3.1; Figure 7; low-certainty evidence). Results were similar when including inferred cases of recurrence reported by Pavesio 2010 (Analysis 3.2), or when considering data reported at six months (Analysis 3.2).

Figure 7. Forest plot of comparison 3: Steroid implant versus standard-of-care, outcome: 3.1 Proportion of eyes with recurrence of uveitis. Pavesio 2010 included one study eye per participant whereas Kempen 2011 included one or two affected eyes into the trial and reported at the eye level.



Footnotes

(1) FAi 0.59 mg, at 24 months, eye was unit of analysis; % of residual uveitis
(2) FAi 0.59 mg, at 24 months, primary efficacy time point
(3) FAi 0.59 mg, at 6 months; derived from Kaplan-Meyer curve
(4) FAi 0.59 mg, at 6 months; % of residual uveitis

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

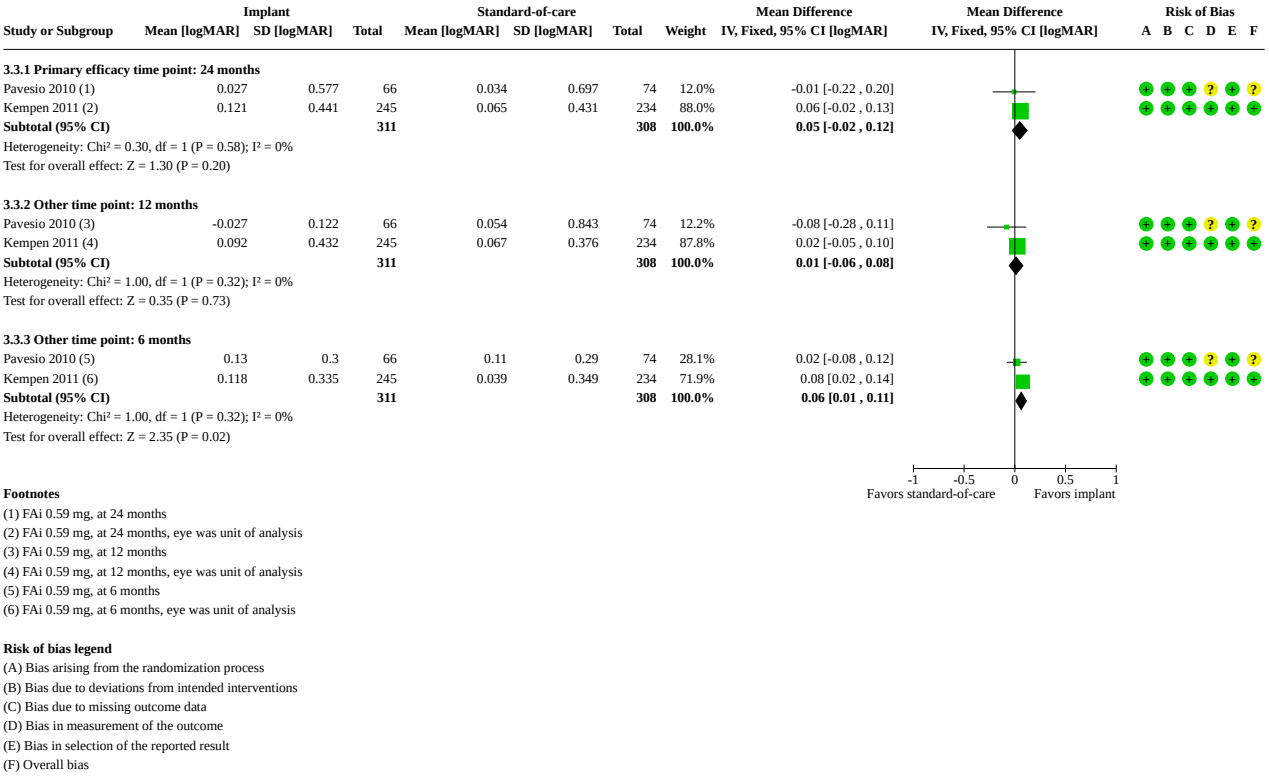
We downgraded the certainty of the evidence for risk of bias (-1) and indirectness (-1), due to a different outcome definition in Kempen 2011.

Important outcomes

Mean difference in BCVA

Both Kempen 2011 and Pavesio 2010 reported the mean improvement in BCVA at 12 and 24 months. Based on combined estimates at the 24-month primary study time point, steroid implants may have little to no effects on improving BCVA compared with standard-of-care therapies (MD 0.05, 95% CI -0.02 to 0.12; 2 trials, 619 eyes; Analysis 3.3; Figure 8; low-certainty evidence). Findings were similar for the 12-month secondary time point, but was significant for minimal BCVA improvement in the steroid implant group at the 6-month secondary time point (Analysis 3.3). We downgraded the certainty of the evidence for risk of bias (-1) and imprecision (-1).

Figure 8. Forest plot of comparison 3: Steroid implant versus standard-of-care, outcome: 3.3 Improvement in BCVA in logMAR. Pavesio 2010 included one study eye per participant whereas Kempen 2011 included one or two affected eyes into the trial and reported at the eye level.



Footnotes
(1) FAi 0.59 mg, at 24 months
(2) FAi 0.59 mg, at 24 months, eye was unit of analysis
(3) FAi 0.59 mg, at 12 months
(4) FAi 0.59 mg, at 12 months, eye was unit of analysis
(5) FAi 0.59 mg, at 6 months
(6) FAi 0.59 mg, at 6 months, eye was unit of analysis

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Mean difference in quality of life scores

Only one trial reported on quality of life (QoL) scores, using the NEI-VFQ25 questionnaire, the SF-36 physical functioning and mental well-being subscales (general health-related quality of life), the EuroQoL EQ-VAS scores, and the EuroQoL EQ-5D scores (Kempen 2011). The reported MCID for each of these QoL scales is: four to six points for the NEI-VFQ25 (Mangione 2001); three to five points for the SF-36 physical and mental subscales (Hays 2001); seven points for the EuroQoL (Pickard 2007); and 0.06 to 0.07 points for the EuroQoL-5D (Pickard 2007).

The single-study (N = 232) estimate suggested that the corticosteroid implant may increase the NEI-VFQ25 score by 4.64 points (95% CI 0.13 to 9.15; Analysis 3.4) more than standard-of-care. Results of the two SF-36 subscales were similarly improved in the implant group, compared with the control group. However, there was no evidence of differences in EuroQoL EQ-VAS or EuroQoL EQ-5D scores between the two groups, either clinically or statistically (Analysis 3.4). In general, corticosteroid implants likely increased participants' quality of life (moderate-certainty evidence). We downgraded the certainty of evidence for imprecision (-1).

Adverse events

Proportion of participants (or eyes) with cataract formation, progression, or participants with phakic eyes that required cataract extraction surgery

- ***Cataract formation***: neither of the two trials reported on this outcome.
- ***Cataract progression***: combined results of 24-month follow-up data suggested that a corticosteroid implant may increase the risk of cataract progression in phakic eyes by 2.71 times of those receiving standard-of-care (RR 2.71, 95% CI 2.06 to 3.56; 2 trials, 210 eyes; Analysis 2.2; low-certainty evidence). Steroid implants may increase the risk of phakic eyes that underwent surgery by 2.98 times (RR 2.98, 95% CI 2.33 to 3.79; 2 trials, 371 eyes; Analysis 2.3; low-certainty evidence; Figure 5). We downgraded the certainty of the evidence for indirectness (-1) and imprecision (-1).

Proportion of participants (or eyes) with elevated IOP > 10 mmHg from baseline or receiving intervention (eye drops or surgery)

- ***Elevated IOP***: evidence from combined results suggested that corticosteroid implants likely increased participants' risk of elevated IOP (> 10 mmHg from baseline) by 3.64 times over those in the standard-of-care group (RR 3.64, 95% CI 2.71 to 4.87; 2 trials, 605 eyes; Analysis 2.4; moderate-certainty evidence).
- ***Elevated IOP requiring intervention***: when compared to standard-of-care, evidence also showed that steroid implants likely resulted in two times higher risk of IOP elevation that required topical medication (RR 3.04, 95% CI 2.36 to 3.91; 2

trials, 544 eyes; Analysis 2.5; moderate-certainty evidence), or four times higher risk of requiring surgical intervention (RR 5.43, 95% CI 3.12 to 9.45; 2 trials, 599 eyes; Analysis 2.6; moderate-certainty evidence; Figure 6).

We downgraded the certainty of the evidence for imprecision (-1).

Proportion of participants (or eyes) with endophthalmitis

Based on combined results, evidence suggested that corticosteroid implants may or may not increase the risk of post-injection endophthalmitis compared with standard-of-care (RR 7.30, 95% CI 0.91 to 58.72; 2 trials, 607 at-risk eyes; Analysis 2.7; moderate-certainty evidence). We downgraded the certainty of the evidence for imprecision (-1).

Proportion of participants (or eyes) with retinal tear or retinal detachment

Evidence based on combined results suggested that steroid implants probably did not increase the risk for retinal tear or retinal detachment compared with standard-of-care (RR 2.07, 95% CI 0.51 to 8.40; 2 trials, 606 at-risk eyes; Analysis 2.8; moderate-certainty evidence). We downgraded the certainty of the evidence for imprecision (-1).

Proportion of participants with systemic adverse events related to steroid or immunomodulatory therapy

Pavesio 2010 reported the risks of overall non-ocular treatment-related adverse events for the FA implant group (0%) and the standard-of-care therapy group (25.7%). They also reported the risks of non-ocular severe adverse events for the implant group (0%) and the standard-of-care group (4.1%), without detailing the specific events that were considered to be treatment-related.

Kempen 2011 reported the risks they considered potential systemic complications for steroid or immunosuppressive therapy separately.

- ***Potential complications of steroid therapy***: the incidence rates of hyperlipidemia (≥ 160 mg/mL); hyperlipidemia requiring treatment; diabetes; or bone osteopenia, porosis, or fracture were comparable between the two groups. The incidence of hypertension, defined by either elevated systolic (≥ 160 mmHg) or diastolic blood pressure (≥ 100 mmHg) was lower in the implant group (2.9 events per 100 person-years) than in the control group (10.3 events per 100 person-years, P for hazard ratio = 0.030). Nevertheless, the risk of new hypertension that required treatment was similar in both groups.
- ***Potential complications of immunosuppressive therapy***: no evidence suggested that the incidence of leukocytopenia (≤ 2500 cells/µL), thrombocytopenia (≤ 100,000/µL), anemia (≤ 10 g/dL), elevated liver enzymes, or serum creatinine levels was different in the two comparison groups.

Overall, the evidence suggested that corticosteroid implants may not increase the risks of systemic adverse events when compared with standard-of-care therapy.

DISCUSSION

Summary of main results

In this update, we reported outcome data from four randomized controlled trials (RCTs) that compared local corticosteroid implants against either sham injection or standard-of-care systemic therapy in the treatment of non-infectious uveitis affecting the posterior segment (NIPU). We analyzed data separately, based on the comparator therapy.

Two trials compared corticosteroid implants with sham injection. One trial evaluated a short-acting implant (0.7 mg dexamethasone) that released corticosteroid for approximately three months, while the other evaluated a long-acting implant (0.18 mg fluocinolone acetonide [FA]) that released corticosteroid for approximately 36 months. Low-certainty evidence suggested that these corticosteroid implants were likely to reduce the risk of uveitis recurrence and to improve best-corrected distance visual acuity (BCVA) at the six-month primary time point compared with sham injection. Low-certainty evidence showed higher rates of local adverse events in the corticosteroid implant groups for cataract formation, with higher risks of intraocular pressure (IOP) elevation, and the need for IOP-lowering medications in the corticosteroid implant group. The relatively short follow-up period for participants in Lowder 2011 may have limited the ability to detect cataract progression. Single-study estimates for quality of life showed comparable changes at six months between the two comparison groups.

Two trials compared corticosteroid implants with standard-of-care systemic therapy. Both studies evaluated a long-acting surgically-placed implant (0.59 mg FA) that released corticosteroid for approximately 30 months. Low-certainty evidence suggested that these corticosteroid implants may reduce the risk of uveitis recurrence and probably improve BCVA at the 24-month primary time point compared with standard-of-care therapy. Low-certainty evidence also showed higher risks of local adverse events in the corticosteroid implant groups for cataract formation and cataract progression, with higher risks of IOP elevation, and the need for medical or surgical interventions to lower IOP after receiving the steroid implants. Single-study estimates from Kempen 2011 reported a lower incidence of hypertension in the implant group, but suggested comparable rates of diabetes, osteoporosis, blood count abnormalities, liver function, or serum creatinine abnormalities.

Overall completeness and applicability of evidence

In all the included trials, the majority of participants were described as White, potentially decreasing the applicability to non-White populations. In this update, we continued the broadened eligibility criteria to include participants under 18 years of age. Both trials comparing 0.59 mg FA to standard-of-care evaluated slightly different populations; Pavesio 2010 enrolled participants with inactive uveitic disease, whereas Kempen 2011 enrolled participants with active disease. Since the primary outcome was evaluated at 24 months, we considered that the influence of this baseline difference on treatment effects was clinically trivial.

The corticosteroid implants evaluated in these four trials (0.59 mg FA, 0.7 mg dexamethasone, and 0.18 mg FA) are three of the four implants that are approved for the treatment of NIPU. The fourth implant, 0.19 mg FA, is thought to have essentially the same characteristics as the 0.18 mg FA, but is indicated for diabetic macular edema (Testi 2019).

Both comparators of sham therapy and standard-of-care systemic therapy provided useful data and evidence from different clinical

perspectives. By comparing with sham therapy, the evidence provided baseline effectiveness and adverse effects of the corticosteroid implants per se. The comparator of standard-of-care systemic therapy provided clinically useful data for both severe, active disease, and controlled disease that was treated initially with either local or systemic therapy.

The outcome measures of uveitis recurrence and BCVA were useful, as these are commonly used clinical parameters that are followed for people with NIPU. Despite the relative paucity of evidence on quality of life outcomes, these outcomes were also of high clinical importance, as this information can assist in the shared decision-making process of which anti-inflammatory therapy to initiate. Kempen 2011 reported on various participant-reported quality of life outcomes. The 0.59 mg FA implant was found to result in higher scores compared to standard-of care therapy in visual functioning, and both physical and mental quality of life. However, it is important to note that although these results were statistically significant, the differences were just at or below the minimal clinically important differences, suggesting that these might not be meaningful improvements in quality of life.

Certainty of the evidence

We downgraded outcomes in this review due to imprecision of results, and risk of bias associated with biased outcome measurement or selective reporting. Specifically, we had some concerns about the reporting of the recurrence of uveitis by three trials, and BCVA by two trials. While the nature of the interventions and the comparators, particularly in the standard-of-care group, made complete masking impossible, unmasked assessors or data analysts might have predisposed trials to be at risk of bias in ascertaining or analyzing the outcome data.

Potential biases in the review process

We performed an extensive literature search in multiple electronic databases and trial registries, and handsearched reference lists of the included trials and the excluded studies of the previous review. We used standard Cochrane methodological procedures to avoid potential biases in the review process. We reported all outcomes that were specified in the protocol for this review, or reported that no data were available for specified outcomes.

Agreements and disagreements with other studies or reviews

We identified two recently published reviews on a similar topic (Abdulla 2022; Logan 2016). In Logan 2016, the authors discussed the 0.59 mg FA used in Kempen 2011, and the 0.7 mg DEX implants used in Lowder 2011. The authors also summarized case reports and series describing the successful use of the implant in the treatment of various uveitic diseases. They concluded that the 0.59 mg FA implant was a useful treatment for NIPU, but it was not necessarily superior to systemic therapy, and carried risks of ocular side effects. In regard to the 0.7 mg DEX implant, the authors also described a comparative case series comparing this implant to the 0.59 mg FA implant. Not surprisingly, the 0.7 mg DEX implant had a shorter time to re-treatment compared to the 0.59 mg FA implant. They also summarized retrospective studies that found the 0.7 mg DEX implant was useful in the treatment of uveitic macular edema.

In Abdulla 2022, the authors discussed the 0.7 mg DEX implant, the 0.18 mg FA implant (they combined these data with data from the 0.19 mg FA implant), and the 0.59 mg FA implant. They also summarized data reported by Lowder 2011 and Jaffe 2019. They spent comparatively little time discussing the 0.59 mg FA implant, as they argued it had "largely been superseded" by the 0.18 and 0.19 mg FA implants. However, they did not discuss the potential differences arising from the fact that the 0.18 mg FA implant releases three-to-four fold less FA than the 0.59 mg FA implant; and while the 0.59 mg FA implant has a fairly steady release rate over three years, the 0.18 mg FA implant releases the drug at a higher rate for the first 12 months and then at a lower rate for the remaining lifespan of the implant (Modugno 2021).

AUTHORS' CONCLUSIONS

Implications for practice

Our confidence is limited that local corticosteroid implants are superior to sham therapy or standard-of-care therapy in reducing the risk of uveitis recurrence in people with non-infectious uveitis.

The included trials exhibited heterogeneity in design, such as the expected dose and product duration of the steroid implants, and in study outcomes, such as the definitions for, and frequency of quantifying core outcomes. Taken together, clinicians and people with chronic non-infectious uveitis must anticipate the possibility of an increased risk of post-implant surgery for cataract progression, or high intraocular pressure (or both), when considering steroid implants as part of a clinical management plan.

Implications for research

With expanded eligibility criteria, we were able to combine efficacy and safety data reported by the included trials. However, high certainty evidence to guide clinical decisions is expected to be informed by trials that

- recruit people with different types of uveitis (chronic posterior uveitis, intermediate uveitis, panuveitis), and then report type-specific treatment effects;
- standardize core outcome measures, such as recurrence of uveitis and time points for efficacy and safety outcomes;
- measure and report person-important outcomes, such as quality of life or visual function-related outcomes.

Given the increased risks for local adverse effects of corticosteroid implants, future trials also need to incorporate participants' perspectives in evaluating the benefit-harm utility of corticosteroid implants as a first-line or second-line treatment option for people with chronic non-infectious uveitis. Results of the three ongoing trials may contribute to the growing evidence of fluocinolone acetonide and dexamethasone, particularly on the treatment benefits. However, future trials that examine head-to-head comparisons of implants with varied drug-releasing rates over time can also provide information on how these steroid implants may achieve persistent anti-inflammatory control without increasing short- or long-term adverse events.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Jaffe 2019

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial

Jaffe 2019 *(Continued)*

Study duration: August 2013 to October 2019

Unit of randomization: person (one eye per person)*

Masking of participants, treatment allocator, outcome assessor, or data analyzor: participants, outcome assessors, and other study personnel were masked

Study visits and time points: screening (day -30 to 0), days 1, 7, 28; months 2, 3, 6, 9, 12, 18, 24, 30, 36

Follow-up duration: 3 years

Planned treatment duration (for standard-of-care arm): NA

Numbers of participants lost or excluded after randomization: none lost to follow-up by the primary efficacy time points at month 6; one and two participants in the FAi and sham group discontinued through month 12

How missing data were handled: "a recurrence event was imputed if, for a previously nonrecurrent study eye, the study eye was treated with a prohibited local or systemic medication, or the participant had a missing ophthalmic assessment at the 6- or 12-month visit".

Power and sample size calculation: "The study sample size of 120 participants (80 and 40 patients for FA insert and sham treatment groups, respectively) was calculated based on the primary end point; treatment groups were not sized to detect statistically significant differences in secondary end points."

***Note:** "The affected eye in unilateral uveitis, the more seriously affected eye in bilateral uveitis, and the right eye in equally affected, symmetrical uveitis were identified as the study eyes".

Participants	**Countries:** 6 countries (USA, Germany, Hungary, India, Israel, UK) **Setting: multicenter** (33 clinical sites [in publication], 34 sites [on clinicaltrials.gov]) **Interventions** • **Implant group:** FA 0.18 mg Age, mean ± SD (range): 48.3 ± 13.9 Female, n (%): 50 (57.5%) Predominant race/ethnicity, n (%): White, 60 (69.0%) Diagnosis of posterior uveitis, n (%): 87 (100%) Number using systemic treatment at baseline, n (%): 44 (50.6%) Participants (eyes) randomized: 87 Participants (eyes) analyzed for efficacy outcome(s): 87 Participants (eyes) analyzed for safety outcome(s): 87 • **Comparison group:** sham procedure Age, mean ± SD (range): 48.3 ± 13.7 Female, n (%): 29 (69.0%) Predominant race/ethnicity, n (%): White, 26 (61.9%) Diagnosis of posterior uveitis, n (%): 42 (100%) Number using systemic treatment at baseline, n (%): 21 (50.0%) Participants (eyes) randomized: 42 Participants (eyes) analyzed for efficacy outcome(s): 42 Participants (eyes) analyzed for safety outcome(s): 42 • **Overall** Age, mean ± SD (range): 48.3 ± 13.8 Female, n (%): 79 (61.2%) Predominant race/ethnicity, n (%): White, 86 (66.7%) Diagnosis of posterior uveitis, n (%): 129 (100%)

Jaffe 2019 *(Continued)*

Number using systemic treatment at baseline, n (%): 65 (50.4%)
Participants (eyes) randomized: 129
Participants (eyes) analyzed for efficacy outcome(s): 129
Participants (eyes) analyzed for safety outcome(s): 129

Inclusion criteria

1. Age 18 years or older
2. Diagnosis of noninfectious uveitis affecting the posterior segment of at least 1 eye (with or without anterior uveitis) for a minimum of 1 year
3. Had experienced at least 2 separate recurrences of uveitis requiring systemic corticosteroid or immunosuppressant treatment or intraocular or periocular corticosteroid injections, or had received in the 12 months preceding study entry (1) systemic therapy (corticosteroid or other systemic treatment) for a minimum of 3 months or (2) at least 2 intraocular or periocular corticosteroid injections to manage uveitis
4. Vitreous haze grade ≥ 25; < 10 anterior chamber cells/high power field determined by slit lamp examination; visual acuity of ≥ 15 letters on the early treatment diabetic retinopathy study (ETDRS) chart visual acuity

Exclusion criteria

1. History of anterior uveitis only (without associated uveitis affected the posterior segment
2. Vitreous hemorrhage
3. Uveitis with infectious etiology
4. Intraocular inflammation associated with a condition other than noninfectious uveitis (e.g. intraocular lymphoma)
5. Any form of glaucoma or ocular hypertension in the study eye at screening (unless the eye was surgically stabilized, returning intraocular pressure [IOP] to within the normal range of 10 mmHg to 21 mmHg)
6. IOP > 21 mmHg or concurrent therapy at screening with any IOP-lowering pharmacologic agent in the study eye
7. Ocular surgery or periocular or sub-Tenon steroid treatment on the study eye within 3 months of day 1

Baseline comparison
"Overall, average disease duration was greater in the FA insert group when compared to the sham group (7.8 vs 5.6 years, respectively), and the proportion of FA insert group participants with disease duration greater than 5 years was nearly twice that observed in the sham group. A lower proportion of FA insert than sham injection study eyes (45% vs 50%, respectively) had a vitreous haze severity of 1/2+."

Interventions

- **FA implant:** FA 0.18 mg was contained in the core of a polyamide polymeric cylinder (3.5 mm long with a 0.37 mm outer diameter) with an impermeable silicon cap on one end and a permeable polyvinyl alcohol membrane on the other end. After placement, drug was delivered through the permeable end of the cylinder at an approximate initial rate of 0.2 mg FA daily, decreasing to 0.1 mg daily over the 36-month study period.
- **Sham procedure:** the sham applicator was an empty 1 ml syringe to which a blunt 18 gauge needle was attached.

Outcomes

Primary outcome of the study:

1. Difference between study groups in the proportion of participants who showed recurrence of uveitis by month 6

Secondary outcomes of the study: treatment group comparisons through 12 months

1. Recurrence rate
2. Cumulative number of recurrences
3. Time to first recurrence
4. BCVA change from baseline

Jaffe 2019 *(Continued)*

	5. Resolution of macular edema (clinical assessment based on OCT imaging) 6. Number of adjunctive treatments used
Notes	**Funding sources:** "Supported by EyePoint Pharmaceuticals, Inc., Watertown, Massachusetts; and the National Institutes of Health, Bethesda, Maryland (S.F.). The sponsor participated in the design of the study, study conduct, data collection, data management, data analysis and interpretation, and preparation and review of the manuscript." **Declaration of interest:** GJJ: consultant - AbbVie, Inc. (North Chicago, IL), Alcon Laboratories (Fort Worth, TX), Novartis Pharma AG (Basel, Switzerland), Neurotech USA, Inc. (Lincoln, RI), Heidelberg Engineering (Heidelberg, Germany). C.S.F.: Consultant - Abbott Laboratories (Lake Bluff, IL), Alcon Laboratories (Fort Worth, TX), Allergan (Dublin, Ireland), Bausch & Lomb (Rochester, NY), EyeGate Pharmaceuticals, Inc. (Waltham, MA), Genentech, Inc. (South San Francisco, CA), Inotech Bioscience (Rockville, MD), Inspire Pharmaceuticals, Inc. (Durham, NC), Ista Pharmaceuticals, Inc. (Irvine, CA), LUX Biosciences, Inc. (Jersey City, NJ), Merrimack Pharmaceuticals, Inc. (Cambridge, MA), Novartis Pharmaceuticals Corporation (East Hanover, NJ), Sirion Therapeutics, Inc. (Tampa, FL), Therakine (Hermosa Beach, CA) CEP: consultant - Allergan (Dublin, Ireland), Alimera Sciences (Alpharetta, GA), EYEVENSYS (Paris, France), Servier Laboratories (Suresnes, France), Santen Pharmaceutical Co., Ltd. (Japan), AbbVie, Inc.(North Chicago, IL) DAP: employee - EyePoint Pharmaceuticals, Inc. (Watertown, MA) GER: employee - EyePoint Pharmaceuticals, Inc. (Watertown, MA) **Trial registry:** NCT02746991 (clinicaltrials.gov) **Publication language:** English **Contact information:** Glenn J. Jaffe, MD; Department of Ophthalmology, Duke University

Kempen 2011

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial (superiority trial) **Study duration:** December 2005 to December 2008 **Unit of randomization:** "Patients were randomized to implant or systemic therapy; patients with bilateral uveitis were assigned to receive implants in each eye meeting eligibility criteria".* **Masking of participants, treatment allocator, outcome assessor, or data analyzor:** "Other than at the 1- and 3-month visits, when postoperative signs were expected to be visible, visual acuity examiners were masked". "Reading Center image evaluations for ocular sequelae of uveitis and of therapy, and glaucoma assessments all were masked. Patients, clinicians, and coordinators were not masked". **Study visits and time points:** "Patients completed study visits at baseline, 1 month, 3 months, and then every 3 months for at least 24 months (contiguous visit windows)." **Follow-up duration:** 24 months for efficacy outcomes **Planned treatment duration (for standard-of-care arm):** "Most cases had active inflammation at baseline and received 1 mg/kg/day up to 60 mg/day of prednisone until either the uveitis was controlled or 4 weeks had elapsed". **Numbers of participants lost or excluded after randomization:** 4 in each group did not complete the 2-year follow-up ; 7 and 8 in the FAi and SOC group were lost prior to 2-year follow-up **How missing data was handled:** "All available visit information was incorporated into the model, with missing data indicators used to maintain the data structure".

Kempen 2011 *(Continued)*

	Power and sample size calculation: "By assuming bilateral disease in 67% of patients, a between-eye correlation of 0.4, a standard deviation of 16 letters' change over 2 years, and a 2-sided type 1 error rate of 0.05, a sample size of 250 provided 91% power (assuming 10% crossover) to detect a treatment difference of 7.5 standard Early Treatment of Diabetic Retinopathy Study letters' change in visual acuity from baseline to 24 months, a difference similar to that which drove widespread use of expensive new retinal treatments in other trials that tested them. One interim analysis using the O'Brien-Fleming-spending function was conducted; the nominal type 1 error rate was 0.049 for the final analysis." *__Note: "__For participants with unilateral disease (N = 31), the affected eye was the study eye. For participants with asymmetric bilateral disease (N = 224), both eyes were study eyes".
Participants	**Countries:** 3 countries (Australia, United Kingdom, United States) **Setting:** multicenter (23 sites) **Interventions** • **Implant group:** FA 0.59 mg implant Age, mean ± SD (range): 46 ± 15 years Female, n (%): 91 (71%) Predominant race/ethnicity, n (%): White 72 (56%) Diagnosis of posterior uveitis, n (%): 79 (61%) Number using systemic treatment at baseline, n (%): NR Participants (eyes) randomized: 129 (245 eyes) Participants (eyes) analyzed for efficacy outcome(s): 129 (245 eyes) Participants (eyes) analyzed for safety outcome(s): 118 • **Comparison group:** standard-of-care Age, mean ± SD (range): 47 ± 15 years Female, n (%): 100 (79%) Predominant race/ethnicity, n (%): White 70 (56%) Diagnosis of posterior or panuveitis, n (%): 79 (63%) Number using systemic treatment at baseline, n (%): NR Participants (eyes) randomized: 126 (234 eyes) Participants (eyes) analyzed for efficacy outcome(s): 126 (234 eyes) Participants (eyes) analyzed for safety outcome(s): 114 • **Overall** Age, mean ± SD (range): 46.3 ± 15.0 years Female, n (%): 191 (75%) Predominant race/ethnicity, n (%): White 142 (57%) Diagnosis of posterior or panuveitis, n (%): 158 (62%) Number using systemic treatment at baseline, n (%): NR Participants (eyes) randomized: 255 (479 eyes) Participants (eyes) analyzed for efficacy outcome(s): 255 (479 eyes) Participants (eyes) analyzed for safety outcome(s): 232 **Inclusion criteria:** 1. Age 13 years or older 2. Diagnosis of noninfectious intermediate uveitis, posterior uveitis, or panuveitis by a MUST-certified ophthalmologist 3. Active uveitis of a degree for which systemic corticosteroid therapy is indicated in the judgment of a MUST-certified ophthalmologist or such uveitis active within the last 60 days as determined either by examination by a MUST-certified ophthalmologist or by review of ophthalmic medical records by a MUST-certified ophthalmologist

Kempen 2011 *(Continued)*

4. Uveitis with or without an associated systemic disease was acceptable; however, the systemic disease could not be sufficiently active that it dictated therapy with oral corticosteroids or immunosuppressive agents at the time of study entry
5. Best-corrected visual acuity of hand movements or better in at least 1 eye with uveitis
6. Baseline intraocular pressure of 24 mmHg or less in all eyes with uveitis
7. Collection of required baseline data within 10 days before randomization
8. Signed informed consent

Exclusion criteria:

1. Use of a fluocinolone acetonide implant within the last 3 years
2. Diabetes mellitus that is inadequately controlled, according to the best medical judgment
3. A known allergy to a required study medication
4. Uncontrolled glaucoma
5. Advanced glaucomatous optic nerve injury meeting the following criteria: (1) for patients able to undertake a Humphrey visual field analysis, depression of 2 points or more within 10 degrees of fixation by at least 10 dB, mean deviation worse than –15 dB, or both; (2) for patients unable to undertake a Humphrey visual field analysis, vertical cup-to-disc ratio [1]0.9
6. A history of scleritis (because of concerns regarding the potential for scleral melting with local corticosteroid therapy)
7. Presence of an ocular toxoplasmosis scar
8. Pregnancy
9. Current breastfeeding
10. Known human immunodeficiency virus infection or other immunodeficiency disease for which corticosteroid therapy would be contraindicated according to the best medical judgment
11. Patients for whom participation in the trial would constitute a risk exceeding the potential benefits of study participation, in the judgment of the treating physician
12. Medical problems or drug or alcohol dependence problems sufficient to prevent adherence to treatment and study procedures

Baseline comparison: "Baseline demographic and clinical characteristics were distributed similarly between groups (Table 1)"

Interventions	• **FA implant:** surgical FA implant (0.59 mg, Bausch & Lomb, Rochester, NY) placement followed in the first eye within 28 days of randomization and in the second eye (if indicated) within 28 additional days • **Standard-of-care:** systemic therapy followed expert panel guidelines "Most cases had active inflammation at baseline and received 1 mg/kg/day up to 60 mg/day of prednisone until either the uveitis was controlled or 4 weeks had elapsed. After control was achieved, prednisone was tapered per study guidelines. Cases already suppressed at baseline began by tapering from their initial prednisone dose. Immunosuppression was indicated for (1) failure to initially control inflammation using corticosteroids; (2) corticosteroid-sparing in cases consistently reactivating before reaching a prednisone dose of 10 mg/day; and (3) specific high-risk uveitis syndromes. When indicated, clinicians selected the approved immunosuppressant most suitable for each patient; administration and monitoring for toxicity followed guidelines. Uveitis experts regularly monitored treatment regimens for protocol compliance at site visits."
Outcomes	**Primary outcome of the study** 1. Change in best-corrected visual acuity from baseline **Secondary outcomes of the study** 1. Patient-reported quality of life 2. Ophthalmologist-graded uveitis activity 3. Local and systemic complications of uveitis or therapy

Kempen 2011 *(Continued)*

	4. Other (laboratory) outcomes: hyperlipidemia diagnosis requiring treatment, cumulative over 24 months, hypertension diagnosis requiring treatment, cumulative over 24 months, diabetes mellitus, cumulative over 24 months, osteoporosis, cumulative over 24 months, white blood cell count < 2500/microliter, cumulative over 24 months, elevated liver enzymes, cumulative over 24 months, elevated creatinine, cumulative over 24 months, cancer diagnosis over 24 months, death over 24 months
Notes	**Funding sources:** National Eye Institute, Research to Prevent Blindness, Paul and Evanina Mackall Foundation. Bausch and Lomb provided "support to the study in the form of a donation of a limited number of fluocinolone implants to patients who were … uninsured or otherwise unable to pay for the implants" **Declaration of interest** "Dr Kempen is a consultant for Alcon Laboratories, Allergan Pharmaceutical Corporation, Lux Biosciences Inc, and Sanofi Pasteur SA. Dr Jabs is a consultant for Abbott Laboratories, Alcon Laboratories, Allergan Pharmaceutical Corporation, Corcept Therapeutics, Genentech Inc, Genzyme Corporation, GlaxoSmithKline, Novartis Pharmaceutical Corporation, Roche Pharmaceuticals, and Applied Genetic Technologies Corporation. Dr Louis is a consultant for Bristol-Myers Squibb, Medtronic Inc, and the National Institute of Diabetes and Digestive and Kidney Diseases. Dr Thorne is a consultant for Heron Evidence Ltd, and Allergan. Drs Altaweel, Holbrook, and Sugar have no conflicts of interest." **Trial registry:** NCT00132691 (clinicaltrials.gov) **Publication language:** English **Contact information:** John H. Kempen, MD, PhD; Department of Ophthalmology, University of Pennsylvania

Lowder 2011

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial **Study duration:** August 2006 to October 2008 **Unit of randomization:** person (one eye per person)* **Masking of participants, treatment allocator, outcome assessor, or data analyzor:** "Patients were masked with regard to study treatment, and the key efficacy variables were collected and evaluated by follow-up investigators who were also masked with regard to study treatment". **Study visits and time points:** baseline, day 1, day 7, week 3, week 6, week 8, week 12, week 16, week 20, week 26 **Follow-up duration:** 26 weeks **Planned treatment duration (for standard-of-care arm):** NA **Numbers of participants lost or excluded after randomization:** "4 and 5 participants in the DEX implant - 0.7 mg and sham group discontinued after randomization, respectively; 2 in the implant group discontinued because of adverse events" **How missing data were handled:** "Any missing data from weeks 2 through 26 were imputed using the last observation carried forward method". **Power and sample size calculation:** "A sample size of 73 patients for each treatment group was determined to have a 93% power to detect a between-group difference of 23% (DEX implant minus

Lowder 2011 *(Continued)*

sham) in the proportion of patients with a vitreous haze score of 0 (assuming 10% of patients in the sham group would have a vitreous haze score of 0)".

*__Note:__ "Only 1 eye was designated as the study eye. If both eyes were eligible for the study, the right eye was designated as the study eye".

Participants	**Countries:** 18 countries (USA, Australia, Austria, Brazil, Canada, Czech Republic, France, Germany, Greece, India, Israel, South Korea, Poland, Portugal, South Africa, Spain, Switzerland, UK) **Setting: multicenter** (46 sites) **Interventions** • **Implant group:** DEX 0.7 mg Age, mean ± SD (range): 44 ± 14.8 Female, n (%): 46 (59.7%) Predominant race/ethnicity, n (%): White, 47 (61%) Diagnosis of posterior uveitis, n (%): 14 (18%) Number using systemic treatment at baseline, n (%): 20 (26%) Participants (eyes) randomized: 77 Participants (eyes) analyzed for efficacy outcome(s): 77 Participants (eyes) analyzed for safety outcome(s): 77 • **Comparison group:** sham procedure Age, mean ± SD (range): 44 ± 15.0 Female, n (%): 51 (67%) Predominant race/ethnicity, n (%): White, 46 (61%) Diagnosis of posterior uveitis, n (%): 18 (24%) Number using systemic treatment at baseline, n (%): 18 (24%) Participants (eyes) randomized: 76 Participants (eyes) analyzed for efficacy outcome(s): 76 Participants (eyes) analyzed for safety outcome(s): 76 • **Overall** Age, mean ± SD (range): 44 ± 14.9 (calculated) Female, n (%): 97 (63.4%) Predominant race/ethnicity, n (%): White, 93 (60.8%) Diagnosis of posterior uveitis, n (%): 32 (20.9%) Number using systemic treatment at baseline, n (%): 38 (24.8%) Participants (eyes) randomized: 153 Participants (eyes) analyzed for efficacy outcome(s): 153 Participants (eyes) analyzed for safety outcome(s): 153 **Inclusion criteria** 1. Diagnosis of noninfectious intermediate or posterior uveitis 2. Age 18 years or older 3. Vitreous haze score of at least +1.5 4. Best-corrected visual acuity of 10 to 75 ETDRS letters **Exclusion criteria** 1. Active ocular disease or infections 2. Uveitis unresponsive to prior corticosteroid treatment 3. The use of IOP-lowering medications within the last month 4. History of glaucoma, ocular hypertension, or clinically significant IOP elevation in response to corticosteroid treatment 5. IOP more than 21 mmHg at baseline 6. Best-corrected visual acuity less than 34 ETDRS letters in the non-study eye

Lowder 2011 *(Continued)*

	7. Any uncontrolled systemic disease. 8. Participated in a previous trial of the dexamethasone implant. 9. Had used the fluocinolone acetonide implant in the study eye 10. Periocular corticosteroid injection in the study eye 8 weeks or fewer prior to the treatment visit on day 0 11. History of any intravitreal drug injection to the study eye 26 weeks or fewer prior to the treatment visit unless it was triamcinolone acetonide at the dose of 4 mg or less injected 26 weeks or more prior to the treatment visit on day 0 12. Anticipation to initiate or change current doses of systemic corticosteroids or systemic immunosuppression during the first 8 weeks of the study 13. Add in that doses of meds needed to be stable before the study as well? **Baseline comparison:** "There were no notable between-group differences in any demographic or baseline characteristic".
Interventions	• **DEX implant:** the 0.7 mg DEX implant was inserted into the vitreous cavity through the pars plana using a customized, single-use, 22 gauge applicator • **Sham procedure:** the sham procedure followed the same protocol but used a needleless applicator All patients were treated with a topical ophthalmic antibiotic 4 times daily starting 3 days prior to the day of their study procedure (day 0) and continuing for 3 days after the procedure.
Outcomes	**Primary outcome of the study** 1. The amount of vitreous haze that obscured visualization and the proportion of patients with a vitreous haze score of 0 at week 8 **Secondary outcomes of the study:** other outcome measures included 1. The time to a vitreous haze score of 0 (through week 26) 2. The proportion of patients achieving at least 2 units of improvement in vitreous haze score (through week 26) 3. Mean change from baseline in vitreous haze scores (through week 26) 4. BCVA measured using a standardized Early Treatment Diabetic Retinopathy Study protocol, 5. Central macular thickness measured by optical coherence tomography (at selected sites) 6. Safety parameters, including adverse events, IOP assessments, slitlamp biomicroscopy, and ophthalmoscopy. Patients were evaluated at baseline and days 1 and 7, and weeks 3, 6, 8, 12, 16, 20, and 26 posttreatment
Notes	**Funding sources:** Allergan, Inc. "participated in the design of the study, data analysis, and interpretation and supervised the preparation of the manuscript and approved the final version." **Declaration of interest:** "Drs Robinson, Schiffman, Li, Cui, and Whitcup are employees of Allergan, Inc." **Trial registry:** NCT00333814 (clinicaltrials.gov) **Publication language:** English **Contact information:** Careen Lowder, MD; Cleveland Clinic Cole Eye Institute **Contact efforts:** emailed enquiry about numbers of participants who required at least one IOP-lowering medications in the sham group

Pavesio 2010

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial **Study duration:** April 2002 to August 2005 **Unit of randomization:** person (one eye per person)* **Masking of participants, treatment allocator, outcome assessor, or data analyzor:** open-label study **Study visits and time points:** "Subjects in the implant treatment group returned to the study site on day 2, whereas subjects in both treatment groups returned to the study site on week 1 (± 2 days), weeks 4, 8, 12, 18, 24, 30, and 34 (± 1 week), at 1 year, and then every 3 months (± 1 month) thereafter, through 3 years for safety and efficacy assessments." **Follow-up duration:** 24 months for efficacy outcomes; 36 months for safety and efficacy outcomes **Planned treatment duration (for standard-of-care arm):** 6 months before tapering or altering **Numbers of participants lost or excluded after randomization:** 6 randomzied to the FAi group discontinued before receiving the implant; another 8 did not complete the 2-year follow-up (5 in the implant group) **How missing data were handled:** 6 participants who did not receive the implant were excluded from the (modified) ITT analysis **Power and sample size calculation:** "A total enrollment of 150 subjects was planned based on the results of a previous study that suggested that the 1-year recurrence rate for SOC would be approximately 30%, and based on the expectation that the implant would reduce this rate to 10% at 1 year. A sample size of 75 subjects per treatment was determined to have 85% power to detect a difference with respect to the primary end point in a 2-tailed test (α = 0.05)". ***Note:** "For participants with unilateral disease, the affected eye was the study eye. For participants with asymmetric bilateral disease, the study eye was the more severely affected eye".
Participants	**Countries:** 10 countries (France, Germany, Israel, Italy, Portugal, Saudi Arabia, Spain, Switzerland, Turkey, United Kingdom) **Setting:** multicentre (37 sites) **Interventions** • **Implant group:** FA 0.59 mg intravitreal implant Age, mean ± SD (range): 40.4 ± 14.4 (12 to 75) years Female, n (%): 32 (48.5%) Predominant race/ethnicity, n (%): White 60 (90.9%) Diagnosis of posterior uveitis, n (%): NR Number using systemic treatment at baseline, n (%): NR Participants (eyes) randomized: 72 Participants (eyes) analyzed for efficacy outcome(s): 66 Participants (eyes) analyzed for safety outcome(s): 66 • **Comparison group:** standard-of-care Age, mean ± SD (range): 43.1 ± 13.5 (18 to 70) years Female, n (%): 50 (67.6%) Predominant race/ethnicity, n (%): White 64 (86.5%) Diagnosis of posterior uveitis, n (%): NR Number using systemic treatment at baseline, n (%): NR Participants (eyes) randomized: 74 Participants (eyes) analyzed for efficacy outcome(s): 74

Pavesio 2010 *(Continued)*

Participants (eyes) analyzed for safety outcome(s): 74

- **Overall**

Age, mean ± SD (range): 41.8 ± 13.9 (12 to 75) years (calculated)
Female, n (%): 82 (58.6%)
Predominant race/ethnicity, n (%): 124 (88.6%)
Diagnosis of posterior uveitis, n (%): 41 (29.4%) (calculated)
Number using systemic treatment at baseline, n (%): 140 (100%)
Participants (eyes) randomized: 146
Participants (eyes) analyzed for efficacy outcome(s): 140
Participants (eyes) analyzed for safety outcome(s): 140

Inclusion criteria

1. Quiet eyes at the time of treatment. Only eye randomized to implant had to be quiet at the time of surgery. Treatment with either ≥ 0.2 mg/kg daily prednisolone equivalent or ≥ 0.1 mg/kg daily prednisolone equivalent immunosuppressant at the time of randomization was required.
2. Male or non-pregnant female aged ≥ 6 years
3. ≥ 1-year history of recurrent or recrudescent unilateral or asymmetric NIPU not associated with significant systemic activity of any underlying disease
4. More severely affected eyes with ≥ 2 separate recurrences of NIPU and the last episode occurring within 8 months of enrollment
5. More severely affected eyes were treated with systemic therapy for ≥ 1 month: ≥ 0.2 mg/kg daily prednisolone equivalent (≥ 10 mg/kg daily for participants > 50 kg) or ≥ 0.1 mg/kg daily prednisolone equivalent if steroids were given with ½ of the following immunosuppressive agents:
   a. cyclosporine A, methotrexate
   b. cyclophosphamide, tacrolimus
   c. mycophenolate mofetil, azathioprine
6. Less severely affected eyes with:
   a. VA of ≥ 0.7 logMAR (6/30)
   b. Uveitis requiring only periocular injections or no therapy
7. Study eyes at time of enrolment:
   a. VA of ≥ 1.4 logMAR (6/150)
   b. ≤ 10 anterior chamber cells/high-power field and a vitreous haze grade ≤ 2"

Exclusion criteria

1. History of retinal detachment, retinoschisis in the area of implantation
2. Media opacity precluding evaluation of the retina and vitreous
3. Presence or history of uncontrolled IOP while receiving steroid therapy resulting in loss of vision
4. IOP > 25 mmHg requiring at least 2 antiglaucoma medications to be reduced to < 25 mmHg
5. Known allergy or contraindication to fluocinolone acetonide, systemic corticosteroids, or immunosuppressive agents
   a. Chronic use of such agents to manage nonocular disease
6. History of NIPU only or iritis only with no vitreitis, macular edema, vitreous cells, or vitreous haze
7. Infectious cause
8. Vitreous hemorrhage or a toxoplasma scar in the study eye
9. Ocular surgery, trauma affecting the study eye, or both within 3 months before enrollment, or trabeculoplasty or yttrium–aluminum–garnet laser within 1 month of enrolment
10. Monocularity for reasons other than uveitis
11. Positive human immunodeficiency virus test results, pregnancy or lactation
12. Potential for noncompliance, or participation in other clinical studies within 1 month of enrolment"

Baseline comparison: "Subject demographics are shown in Table 2. The 2 treatment groups were similar in age and race, but there was a statistically significant difference between the treatment groups in gender, with 67.6% of SOC subjects being female versus 48.5% of implant subjects being

Pavesio 2010 *(Continued)*

	female (P = 0.02). Baseline values for VA, IOP, and anterior chamber flare, anterior chamber cells, vitreous haze, and incidence of cataracts were similar between the implant and SOC groups".
Interventions	• **FA implant:** surgical implantation of 0.59 mg FA in vitreous cavity • **Standard-of-care:** standard-of-care systemic management of uveitis "The SOC group received prednisolone or an equivalent corticosteroid alone, or an immunosuppressive agent was added to the therapy and the corticosteroid dose was reduced. Levels considered acceptable for therapy with steroids alone were 0.2 mg/kg daily (or 15 mg/day for the average weight). When inflammation could not be controlled with this level of corticosteroid, immunosuppressive agents were added. With the use of an immunosuppressive agent, the objective was to reduce steroid use to 0.1 mg/kg daily of prednisolone equivalent after 4 to 6 weeks of combination therapy. Approved immunosuppressants included cyclosporine A, methotrexate, cyclophosphamide, mycophenolate mofetil, azathioprine, and tacrolimus. If an immunosuppressive agent was not recommended, subjects were managed by maintaining systemic steroids at a higher level (0.2 mg/kg daily of prednisolone equivalent) or by increasing the steroids in case of inflammation. This regimen was followed by a slow taper to a minimal dose of 0.2 mg/kg daily (10 mg/day for subjects whose weight was 50 kg). After 6 months, if the disease was controlled, the treatment doses were tapered according to the standard guideline of each investigational site."
Outcomes	**Primary outcomes of the study** 1. "Time to first recurrence of uveitis occurring in the 24 months after randomization for the standard-of-care group and time to first recurrence of uveitis in the study eye in the 24 months after the week-12 visit for the implant group. The first 12 weeks were excluded from the analysis of implant efficacy to allow prestudy anti-inflammatory agents and postoperative inflammation therapy to be discontinued". **Secondary outcomes of the study** 1. Percentage of participants with at least 1 recurrence 2. Number of recurrences per participant 3. Number of recurrences compared with the number that occurred during the 52 weeks before enrollment 4. Proportion of participants with a VA improvement (> 15 letters on Early Treatment Diabetic Retinopathy Study charts from baseline) 5. If cystoid macular edema present, the change in the size of the area of cystoid macular edema on fluorescein angiography
Notes	**Funding source:** Bausch and Lomb Inc. **Declaration of interest:** Of the 5 study authors, lead author is a consultant for Bausch and Lomb Inc, and 3 authors are employees of Bausch and Lomb Inc. **Trial registry:** NCT00468871 (clinicaltrials.gov) **Publication language:** English **Contact information:** Carlos E. Pavesio, MD, FRCOphth; Moorfields Eye Hospital, London

AE: adverse event
DEX: dexamethasone
FA: fluocinolone acetonide
FAi: fluocinolone acetonide intravitreal (implant/insert)
IOP: intraocular pressure
MUST: Multicenter Uveitis Steroid Treatment
NA: not applicable
NR: not reported
NIPU: non-infectious posterior uveitis
SD: standard deviation

VA: visual acuity

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Acharya 2004	Ineligible design: not an RCT
ACTRN12605000485639	Ineligible comparator: dose-comparing trial
Anonymous 1995	Ineligible design
Ansari 2010	Ineligible design: not an RCT
Arcinue 2013	Ineligible design: not an RCT
Bollinger 2009	Ineligible study population
Callanan 2008	Ineligible comparator: a dose-comparing trial
Callanan 2020	This article was withdrawn at the request of the author(s), editor, or both
Campochiaro 2013	Ineligible study population
Cano-Parra 2006	Ineligible design: not an RCT
Ciulla 2021	Ineligible study population
Cornish 2018	Ineligible design: not an RCT
Couret 2020	Ineligible study population
Eng 2007	Ineligible study population
Ermakova 2003	Ineligible design: not an RCT
Errera 2019	Ineligible design: observational study
Galor 2007	Ineligible design: not an RCT
Garg 2006	Ineligible design: not an RCT
Goldstein 2007	Ineligible design: a pooled analysis of 3 dose-comparing trials
Jaffe 2000a	Ineligible design: an interventional case series
Jaffe 2000b	Ineligible design: a case report
Jaffe 2016	Ineligible comparator: a dose-comparing study
Kim 2011	Ineligible design: not an RCT
Kuppermann 2007	Ineligible study population
Mercante 2007	Ineligible study population
Mustakallio 1973	Ineligible study population

Study	Reason for exclusion
NCT02309385	Ineligible study population
NCT02482129	Ineligible study population
NCT02517619	Ineligible study population
NCT02748512	Ineligible intervention
NCT04976777	Ineligible study population
Neger 1996	Ineligible study population
Novack 2008	Ineligible design: not an RCT
Ram 2013	Ineligible study population
Sangwan 2015	Ineligible comparator: a dose-comparing trial
Taylor 2012	Ineligible study design: case series
Wen 1991	Ineligible intervention
Williams 2009	Ineligible study population

FA: fluocinolone acetonide
FAi: fluocinolone acetonide intravitreal (implant/insert)
mg: milligram
RCT: randomized controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR1900026160

Study name	A phase iii, multicenter, randomized, double-blind, controlled, safety and efficacy study for a fluocinolone acetonide intravitreal (FAi) insert in subjects with chronic non-infectious uveitis affecting the posterior segment of the eye
Methods	Randomzied parallel-group controlled trial
Participants	**Age limitation**: not reported **Gender**: both **Inclusion criteria** 1. Male or non-pregnant female at least 18 years of age at time of consent 2. One or both eyes having a history of recurrent non-infectious uveitis affecting the posterior segment of the eye with or without anterior uveitis ≥ 1 year duration 3. At the time of enrollment (day 1), study eye has < 10 anterior chamber cells /HPF and a vitreous haze ≤ grade 2 4. Visual acuity of study eye is at least 15 letters on the ETDRS chart 5. Subject is not planning to undergo elective ocular surgery during the study 6. Subject has ability to understand and sign the informed consent form 7. Subject is willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures

ChiCTR1900026160 *(Continued)*

Exclusion criteria

1. Allergy to fluocinolone acetonide or any component of the FAi insert
2. History of posterior uveitis only, which is not accompanied by vitritis or macular edema
3. History of iritis only and no vitreous cells, anterior chamber cells, or vitreous haze
4. Uveitis with infectious etiology
5. Vitreous hemorrhage
6. Intraocular inflammation associated with a condition other than noninfectious uveitis
7. Ocular malignancy in either eye, including choroidal melanoma
8. Toxoplasmosis scar in study eye or scar related to previous viral retinitis
9. Previous viral retinitis
10. Current viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, mycobacterial infections of the eye or fungal diseases of the eye
11. Media opacity precluding evaluation of retina and vitreous
12. Peripheral retinal detachment in area of insertion
13. Diagnosis of any form of glaucoma or ocular hypertension in study eye at screening, unless study eye has been previously treated with filtration surgery procedure that has resulted in stable IOP in the normal range (10 mmHg to 21 mmHg)
14. Intraocular pressure (IOP) > 21 mmHg or concurrent therapy at screening with any IOP-lowering drug in the study eye
15. Chronic hypotony (< 6 mmHg)
16. Ocular surgery on the study eye within 3 months prior to study day 1
17. History of vitrectomy
18. Capsulotomy in study eye within 30 days prior to study day 1
19. Prior intravitreal treatment of study eye with Retisert within 36 months prior to study day 1
20. Prior intravitreal treatment of study eye with Ozurdex within 6 months prior to study day 1
21. Prior intravitreal treatment of study eye with Trivaris within 3 months prior to study day 1
22. Periocular or subtenon injection of corticosteroid for treatment of study eye within 3 months prior to study day 1
23. Subjects requiring chronic systemic or inhaled corticosteroid therapy (> 15 mg prednisone daily) or chronic systemic immunosuppressive therapy
24. Skin cancers (specifically, basal cell carcinoma and squamous cell carcinoma), any malignancy receiving treatment, or in remission less than 5 years
25. Subjects who test positive for HIV or syphilis during screening
26. Clinical signs and symptoms of typical active tuberculosis or extrapulmonary tuberculosis, or chest radiographs showing active tuberculosis
27. Strong positive for tuberculin test (PPD test, local red and swelling hard mass with diameter of ≥ 20 mm or local blister, necrosis, lymphangitis), and contact with tuberculosis patients, or suspected tuberculosis symptoms (or both) or signs occurring within 3 months (or both)
28. Mycobacterial uveitis or chorioretinal changes of either eye, which in the opinion of the Investigator, results from infectious mycobacterial uveitis
29. Any severe systemic condition, which in the judgment of the investigator, could limit the subject's entry into the clinical study, including, but not limited to, the following conditions: active infection, uncontrolled diabetes, severe heart disease, etc.
30. Any severe acute or chronic medical or psychiatric condition that could increase the risk associated with study participation or could interfere with the interpretation of study results, and in the judgment of the investigator, could make the subject inappropriate for entry into this study
31. Any systemic or ocular condition

Interventions	Target sample size: 100 in experimental and 50 in control group • Intravitreal FA insert • Sham injection

ChiCTR1900026160 *(Continued)*

Outcomes	Primary outcomes 1. Proportion of subjects who have a recurrence of uveitis in the study eye within 6 months after receiving study treatment Secondary outcomes: not reported
Starting date	01 October 2019 (expected)
Contact information	Contact person: Changdong Liu, Dan Jia; Ocumension Tehrapeutics (Shanghai) Co., Ltd., Shanghai, China Email: dan.jia@ocumension.com (Dan Jia replied that the trial is still ongoing).
Notes	Sources of financial support: fully self-raised Date of last update: 30 September 2019

NCT05070728

Study name	Safety and efficacy of an injectable fluocinolone acetonide intravitreal insert (FAi)
Methods	Randomized parallel-group controlled trial
Participants	**Age limitation**: 18 years and older **Gender**: all **Inclusion criteria** 1. Male or non-pregnant female at least 18 years of age at time of consent 2. One or both eyes having a history of recurrent non-infectious uveitis affecting the posterior segment of the eye (intermediate, posterior, or panuveitis) with or without anterior uveitis > 1 year duration 3. During the 52 weeks prior to enrollment (day 1), the study eye has either received treatment systemic corticosteroid or other systemic therapies given for at least 12 weeks, or at least 2 intra- or periocular injections of corticosteroid, or both, for management of uveitis, or the study eye has experienced recurrence recurrences of uveitis at least 2 separate times requiring systemic, intra- or periocular injection of corticosteroid 4. Subject is not planning to undergo elective ocular surgery during the study 5. Subject has ability to understand and sign the informed consent form (ICF) 6. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures 7. Other protocol-specified inclusion criteria may apply **Exclusion criteria** 1. History of posterior uveitis only that is not accompanied by vitritis or macular edema 2. History of iritis only associated with no vitreous cells, anterior chamber cells, or vitreous haze at day 1 3. Uveitis with infectious etiology 4. Vitreous hemorrhage 5. Intraocular inflammation associated with a condition other than noninfectious uveitis (eg, intraocular lymphoma) 6. Uveitis limited to the anterior segment, i.e. anterior uveitis only 7. Ocular malignancy in either eye, including choroidal melanoma 8. Previous viral retinitis

NCT05070728 *(Continued)*

	9. Requirement for chronic systemic or inhaled corticosteroid therapy (> 15 mg prednisone daily) or chronic systemic immunosuppressive therapy 10. History of certain skin cancers (specifically, basal cell carcinoma and squamous cell carcinoma), any malignancy receiving treatment, or in remission less than 5 years prior to day 1 11. Positive test for HIV or syphilis during screening 12. Mycobacterial uveitis or chorioretinal changes of either eye, which in the opinion of the Investigator, resulting from infectious mycobacterial uveitis 13. Systemic infection within 30 days prior to day 1 14. Pregnant or nursing females; females of childbearing potential who are unwilling or unable to use an acceptable method of contraception as outlined in the protocol from at least 14 days prior to day 1 until the 52-week visit 15. Other protocol-specified exclusion criteria may apply
Interventions	Target sample size: 60 in total • FA insert (0.05 mg FA) • Sham injector
Outcomes	Primary outcome: 1. Proportion of subjects who have a recurrence of uveitis in the study eye within 24 weeks (6 months) after receiving study treatment [time frame: 24 weeks]
Starting date	17 November 2021
Contact information	Contact person: Dario Paggiarino, MD Email: dpaggiarino@eyepointpharma.com
Notes	Sponsors and collaborators: EyePoint Pharmaceuticals, Inc.

NCT05101928

Study name	Ozurdex monotherapy trial (OM)
Methods	randomized parallel-group controlled trial
Participants	**Age limitation:** 18 years and older **Sex**: all **Inclusion criteria** 1. Age ≥ 18 years 2. Diagnosis of non-infectious intermediate, posterior, or panuveitis in at least one eye 3. Active uveitic disease at screening or baseline defined by the presence of at least 1 of the following parameters: 1) active, inflammatory, chorioretinal, or inflammatory retinal vascular lesion, or a combination, 2) ≥ 1+ vitreous haze (NEI/SUN criteria) **Exclusion criteria** 1. Presence of isolated anterior uveitis 2. Evidence of macular edema due to diabetes, retinal vein occlusion, or any other ocular conditions 3. Confirmed or suspected active ocular disease or infections 4. Intraocular surgery in the past 6 months 5. History of glaucoma

NCT05101928 *(Continued)*

	6. Intraocular pressure (IOP) of > 21 mmHg at screening or baseline, or confirmed normal-tension glaucoma 7. Intravitreal or periocular injection within 6 months prior to screening 8. Unable to tolerate systemic corticosteroids 9. Prior topical corticosteroid within 1 month of screening 10. Prior non-steroidal anti-inflammatory, systemic steroids, or immunomodulatory therapy (e.g. methotrexate) within 1 month of screening 11. For women: pregnant or breastfeeding, or planning to become pregnant while enrolled in the study
Interventions	Target sample size: 84 in total • Ozurdex 0.7mg ophthalmic implant (DEX, Allergan, Inc. Irvine, CA) • Prednisone (oral)
Outcomes	Primary outcomes: 1. Percentage of patients with vitreous haze score of 0 at 6 months [time frame: measurements obtained at 6 months] Secondary outcomes: 1. Best Corrected Visual Acuity at various time points [time frame: measurements obtained at: 1 month, 2 months, 4 months, 6 months, 12 months] 2. Proportion of patients with vitreous haze improvement by 1 and 2 units from baseline to various time points [time frame: measurements obtained at: 1 month, 2 months, 4 months, 6 months, 12 months] 3. Time to vitreous haze score of 0 from baseline to various time points [time frame: measurements obtained at: 1 month, 2 months, 4 months, 6 months, 12 months] 4. Anterior chamber cells/flare from baseline to various time points [time frame: measurements obtained at: 1 month, 2 months, 4 months, 6 months, 12 months] 5. Change in central average thickness (µm) from baseline to various time points [time frame: measurements obtained at: 1 month, 2 months, 4 months, 6 months, 12 months] 6. Change in central average volume (in mm^3) from baseline to various time points [time frame: measurements obtained at: 1 month, 2 months, 4 months, 6 months, 12 months] 7. Change in National Eye Institute Visual Function Questionnaire 25 score [time frame: baseline and 12 mo] 8. Incidence of complications [time frame: anywhere between baseline and 12 months] 9. Percentage of patients with vitreous haze score of 0 at various time points [time frame: measurements obtained at: 1 month, 2 months, 4 months, 6 months (primary outcome), 12 months]
Starting date	1 December 2021 (expected)
Contact information	Contact person: Melanie Lalonde, PhD Email: mlalonde@ohri.ca
Notes	Sponsors and collaborators: Ottawa Hospital Research Institute

DEX: dexamethasone
FA: fluocinolone acetonide
FAi: fluocinolone acetonide intravitreal (implant/insert)
OM: Ozurdex monotherapy

RISK OF BIAS

Legend: ✓ Low risk of bias ✗ High risk of bias ~ Some concerns

Risk of bias for analysis 1.1 Proportion of participants with recurrence of uveitis

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.1.1 Primary efficacy time point: 6 months						
Jaffe 2019	✓	✓	✓	✓	✓	✓
Lowder 2011	✓	✓	✓	✓	~	~
Subgroup 1.1.2 Other time point: 12 months						
Jaffe 2019	✓	✓	✓	✓	✓	✓
Subgroup 1.1.3 Other time point: 36 months						
Jaffe 2019	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.2 Improvement in BCVA [logMAR]

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.2.1 Primary efficacy time point: 6 months						
Lowder 2011	✓	✓	✓	✓	~	~
Subgroup 1.2.2 Other time point: 12 months						
Jaffe 2019	✓	✓	✓	✓	✓	✓
Subgroup 1.2.3 Other time point: 36 months						
Jaffe 2019	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.1 Proportion of eyes with recurrence of uveitis

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.1.1 Primary efficacy time point: 24 months						
Kempen 2011	✓	✓	✓	~	✓	~
Pavesio 2010	✓	✓	✓	~	✓	~
Subgroup 3.1.2 Other time point: 6 months						
Pavesio 2010	✓	✓	✓	~	✓	~
Kempen 2011	✓	✓	✓	~	✓	~

Risk of bias for analysis 3.2 Proportion of eyes with recurrence of uveitis; sensitivity analysis

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.2.1 Primary efficacy time point: 24 months						
Kempen 2011	✓	✓	✓	~	✓	~
Pavesio 2010	✓	✓	✓	~	✓	~
Subgroup 3.2.2 Other time point: 6 months						
Pavesio 2010	✓	✓	✓	~	✓	~
Kempen 2011	✓	✓	✓	~	✓	~

Risk of bias for analysis 3.3 Improvement in BCVA [logMAR]

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.3.1 Primary efficacy time point: 24 months						
Pavesio 2010	✓	✓	✓	~	✓	~
Kempen 2011	✓	✓	✓	✓	✓	✓
Subgroup 3.3.2 Other time point: 12 months						
Pavesio 2010	✓	✓	✓	~	✓	~
Kempen 2011	✓	✓	✓	✓	✓	✓
Subgroup 3.3.3 Other time point: 6 months						
Pavesio 2010	✓	✓	✓	~	✓	~
Kempen 2011	✓	✓	✓	✓	✓	✓

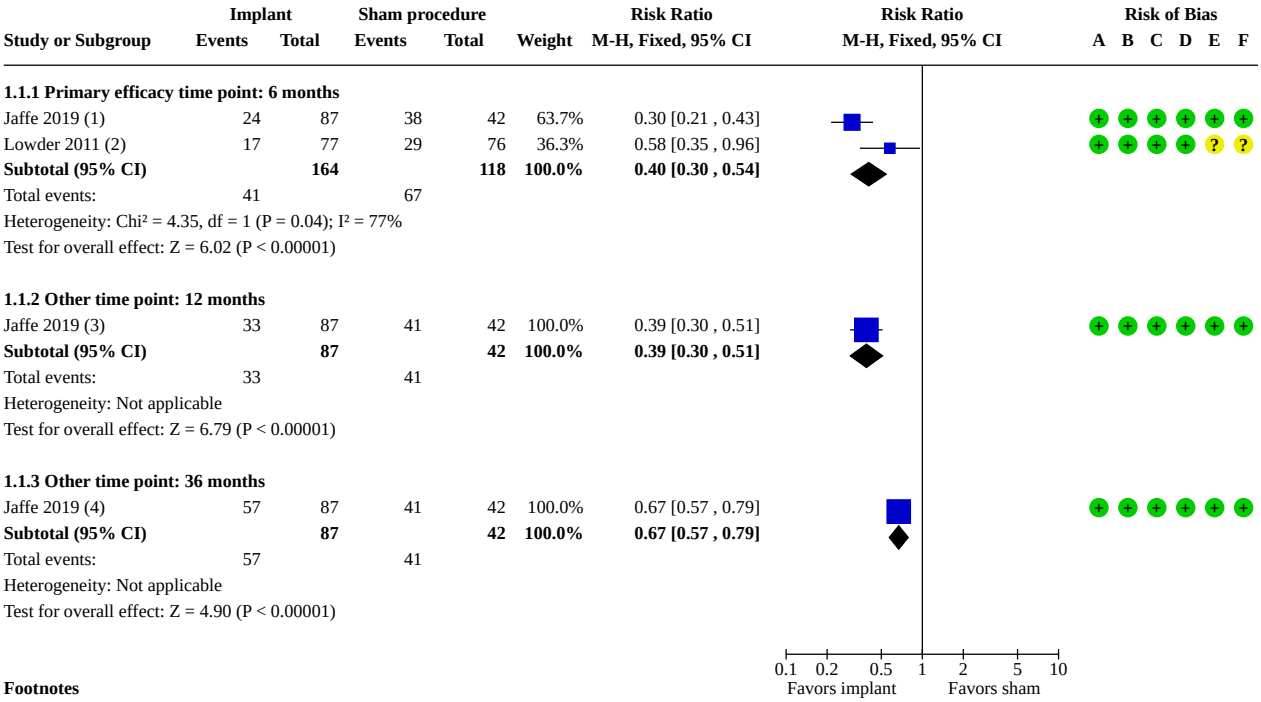
DATA AND ANALYSES

Comparison 1. Steroid implant vs sham procedure

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Proportion of participants with recurrence of uveitis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1.1 Primary efficacy time point: 6 months	2	282	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.30, 0.54]
1.1.2 Other time point: 12 months	1	129	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.30, 0.51]
1.1.3 Other time point: 36 months	1	129	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.57, 0.79]
1.2 Improvement in BCVA [logMAR]	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2.1 Primary efficacy time point: 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.2 Other time point: 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2.3 Other time point: 36 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3 Mean difference in quality of life scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Steroid implant vs sham procedure, Outcome 1: Proportion of participants with recurrence of uveitis



Footnotes

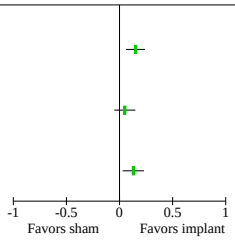
(1) FAi 0.18 mg, at 6 months
(2) DEX 0.4 mg, at 26 weeks
(3) FAi 0.18 mg, at 12 months
(4) FAi 0.18 mg, at 36 months

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: Steroid implant vs sham procedure, Outcome 2: Improvement in BCVA [logMAR]

Study or Subgroup	Implant Mean [logMAR]	Implant SD [logMAR]	Implant Total	Sham procedure Mean [logMAR]	Sham procedure SD [logMAR]	Sham procedure Total	Mean Difference IV, Fixed, 95% CI [logMAR]	Risk of Bias A B C D E F
1.2.1 Primary efficacy time point: 6 months								
Lowder 2011 (1)	0.22	0.28	77	0.07	0.28	76	0.15 [0.06 , 0.24]	+ + + + ? ?
1.2.2 Other time point: 12 months								
Jaffe 2019 (2)	0.12	0.29	87	0.07	0.26	42	0.05 [-0.05 , 0.15]	+ + + + + +
1.2.3 Other time point: 36 months								
Jaffe 2019 (3)	0.18	0.26	87	0.05	0.28	42	0.13 [0.03 , 0.23]	+ + + + + +

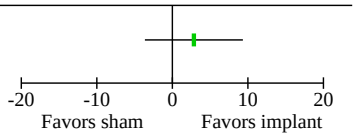


Footnotes
(1) DEX 0.7 mg, at 6 months
(2) FAi 0.18 mg, at 12 months
(3) FAi 0.18 mg, at 36 months

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: Steroid implant vs sham procedure, Outcome 3: Mean difference in quality of life scores

Study or Subgroup	Implant Mean	Implant SD	Implant Total	Sham procedure Mean	Sham procedure SD	Sham procedure Total	Mean Difference IV, Fixed, 95% CI
Lowder 2011 (1)	76.23	18.72	73	73.38	21.19	73	2.85 [-3.64 , 9.34]



Footnotes
(1) DEX 0.7 mg, at 26 weeks; post-intervention scores in VFQ25

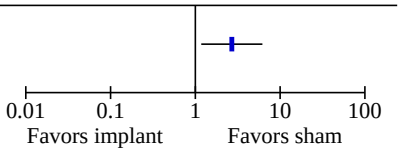
Comparison 2. Steroid implant vs sham procedure: ocular adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Proportion of eyes with cataract formation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.2 Proportion of eyes with cataract progression	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.2.1 Sham procedure	1	117	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.65, 6.12]
2.2.2 Standard-of-care	2	210	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [2.06, 3.56]
2.3 Proportion of eyes that underwent cataract surgery	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.3.1 Sham procedure	2	180	Risk Ratio (M-H, Fixed, 95% CI)	2.98 [0.82, 10.81]
2.3.2 Standard-of-care	2	371	Risk Ratio (M-H, Fixed, 95% CI)	2.98 [2.33, 3.79]
2.4 Proportion of eyes with elevated IOP	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4.1 Sham procedure	2	282	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [1.42, 5.56]
2.4.2 Standard-of-care	2	605	Risk Ratio (M-H, Fixed, 95% CI)	3.64 [2.71, 4.87]
2.5 Proportion of eyes receiving IOP-lowering medications	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.5.1 Sham procedure	2	282	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [1.05, 3.25]
2.5.2 Standard-of-care	2	544	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [2.36, 3.91]
2.6 Proportion of eyes that underwent IOP-lowering surgery	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.6.1 Sham procedure	2	282	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.13, 4.17]
2.6.2 Standard-of-care	2	599	Risk Ratio (M-H, Fixed, 95% CI)	5.43 [3.12, 9.45]
2.7 Proportion of eyes with endophthalmitis	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.7.1 Sham procedure	2	280	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.10, 2.30]
2.7.2 Standard-of-care	2	607	Risk Ratio (M-H, Fixed, 95% CI)	7.30 [0.91, 58.72]
2.8 Proportion of eyes with retinal tear or detachment	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.8.1 Sham procedure	2	280	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.21, 5.75]
2.8.2 Standard-of-care	2	606	Risk Ratio (M-H, Fixed, 95% CI)	2.07 [0.51, 8.40]

Analysis 2.1. Comparison 2: Steroid implant vs sham procedure: ocular adverse events, Outcome 1: Proportion of eyes with cataract formation

Study or Subgroup	Implant Events	Implant Total	Sham procedure Events	Sham procedure Total	Risk Ratio M-H, Fixed, 95% CI
Jaffe 2019 (1)	12	35	7	55	2.69 [1.17 , 6.18]

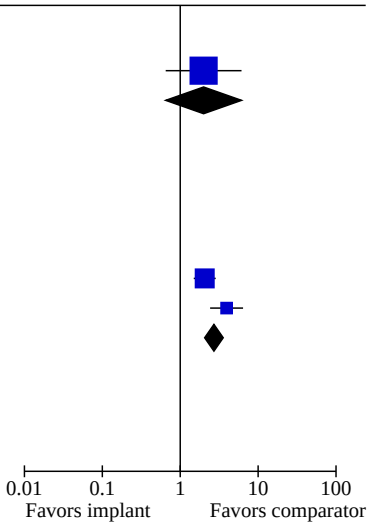


Footnotes

(1) FAi 0.18 mg, at 12 months; denominators were aphakic eyes at baseline

Analysis 2.2. Comparison 2: Steroid implant vs sham procedure: ocular adverse events, Outcome 2: Proportion of eyes with cataract progression

Study or Subgroup	Implant Events	Implant Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Sham procedure						
Lowder 2011 (1)	9	62	4	55	100.0%	2.00 [0.65 , 6.12]
Subtotal (95% CI)		**62**		**55**	**100.0%**	**2.00 [0.65 , 6.12]**
Total events:	9		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.23)						
2.2.2 Standard-of-care						
Kempen 2011 (2)	49	54	22	50	65.5%	2.06 [1.49 , 2.85]
Pavesio 2010 (3)	44	49	13	57	34.5%	3.94 [2.42 , 6.41]
Subtotal (95% CI)		**103**		**107**	**100.0%**	**2.71 [2.06 , 3.56]**
Total events:	93		35			
Heterogeneity: Chi² = 4.99, df = 1 (P = 0.03); I² = 80%						
Test for overall effect: Z = 7.12 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						

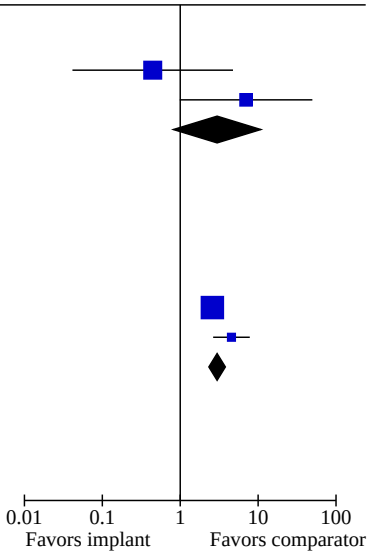


Footnotes

(1) DEX 0.7mg, at 26 weeks, denominators were phakic eyes at baseline
(2) FAi 0.59 mg, at 24 months, denominators were 'at-risk' eyes at baseline
(3) FAi 0.59 mg, at 24 months, denominators were phakic eyes at baseline

Analysis 2.3. Comparison 2: Steroid implant vs sham procedure: ocular adverse events, Outcome 3: Proportion of eyes that underwent cataract surgery

Study or Subgroup	Implant Events	Implant Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Sham procedure						
Lowder 2011 (1)	1	62	2	55	61.4%	0.44 [0.04 , 4.76]
Jaffe 2019 (2)	14	42	1	21	38.6%	7.00 [0.99 , 49.69]
Subtotal (95% CI)		**104**		**76**	**100.0%**	**2.98 [0.82 , 10.81]**
Total events:	15		3			
Heterogeneity: Chi² = 3.20, df = 1 (P = 0.07); I² = 69%						
Test for overall effect: Z = 1.66 (P = 0.10)						
2.3.2 Standard-of-care						
Kempen 2011 (3)	113	140	39	125	80.2%	2.59 [1.97 , 3.40]
Pavesio 2010 (4)	43	49	11	57	19.8%	4.55 [2.65 , 7.81]
Subtotal (95% CI)		**189**		**182**	**100.0%**	**2.98 [2.33 , 3.79]**
Total events:	156		50			
Heterogeneity: Chi² = 3.37, df = 1 (P = 0.07); I² = 70%						
Test for overall effect: Z = 8.79 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						

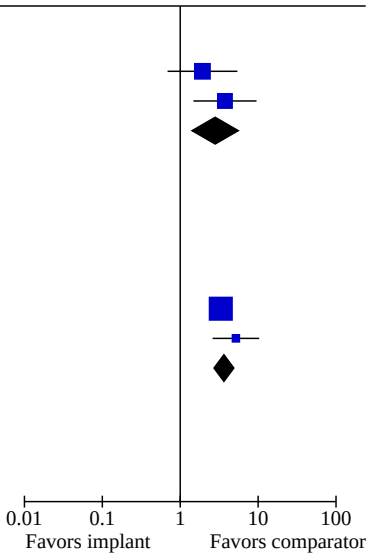


Footnotes

(1) DEX 0.7 mg, at 26 weeks, denominators were phakic eyes at baseline
(2) FAi 0.18 mg, at 12 months, denominators were phakic eyes at baseline
(3) FAi 0.59 mg, at 24 months, denominators were 'at-risk' eyes at baseline
(4) FAi 0.59 mg, at 24 months, denominators were phakic eyes at baseline

Analysis 2.4. Comparison 2: Steroid implant vs sham procedure: ocular adverse events, Outcome 4: Proportion of eyes with elevated IOP

Study or Subgroup	Implant Events	Implant Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Sham procedure						
Jaffe 2019 (1)	16	87	4	42	51.7%	1.93 [0.69 , 5.42]
Lowder 2011 (2)	19	77	5	76	48.3%	3.75 [1.48 , 9.53]
Subtotal (95% CI)		**164**		**118**	**100.0%**	**2.81 [1.42 , 5.56]**
Total events:	35		9			
Heterogeneity: Chi² = 0.88, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 2.96 (P = 0.003)						
2.4.2 Standard-of-care						
Kempen 2011 (3)	122	235	36	230	82.8%	3.32 [2.40 , 4.59]
Pavesio 2010 (4)	37	66	8	74	17.2%	5.19 [2.61 , 10.32]
Subtotal (95% CI)		**301**		**304**	**100.0%**	**3.64 [2.71 , 4.87]**
Total events:	159		44			
Heterogeneity: Chi² = 1.33, df = 1 (P = 0.25); I² = 25%						
Test for overall effect: Z = 8.65 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						

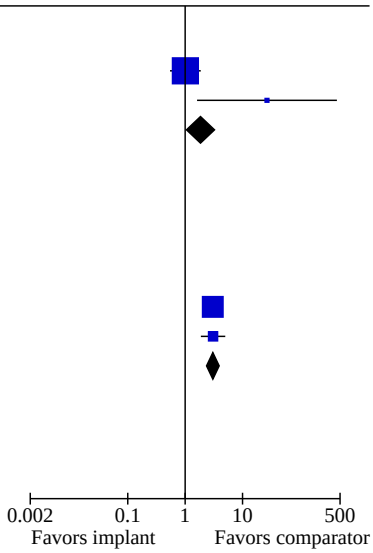


Footnotes

(1) FAi 0.18 mg, at 12 months, IOP elevation > 12 mmHg from baseline
(2) DEX 0.7 mg, at 26 weeks, obtained from clinicaltrials.gov
(3) FAi 0.59 mg, at 24 months, unit of analysis was eye
(4) FAi 0.59 mg, at 24 months

Analysis 2.5. Comparison 2: Steroid implant vs sham procedure: ocular adverse events, Outcome 5: Proportion of eyes receiving IOP-lowering medications

Study or Subgroup	Implant Events	Implant Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.5.1 Sham procedure						
Jaffe 2019 (1)	23	87	11	42	96.7%	1.01 [0.54 , 1.87]
Lowder 2011 (2)	13	77	0	76	3.3%	26.65 [1.61 , 440.53]
Subtotal (95% CI)		**164**		**118**	**100.0%**	**1.85 [1.05 , 3.25]**
Total events:	36		11			
Heterogeneity: Chi² = 7.18, df = 1 (P = 0.007); I² = 86%						
Test for overall effect: Z = 2.15 (P = 0.03)						
2.5.2 Standard-of-care						
Kempen 2011 (3)	123	201	41	203	74.3%	3.03 [2.26 , 4.07]
Pavesio 2010 (4)	41	66	15	74	25.7%	3.06 [1.88 , 5.00]
Subtotal (95% CI)		**267**		**277**	**100.0%**	**3.04 [2.36 , 3.91]**
Total events:	164		56			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 8.63 (P < 0.00001)						

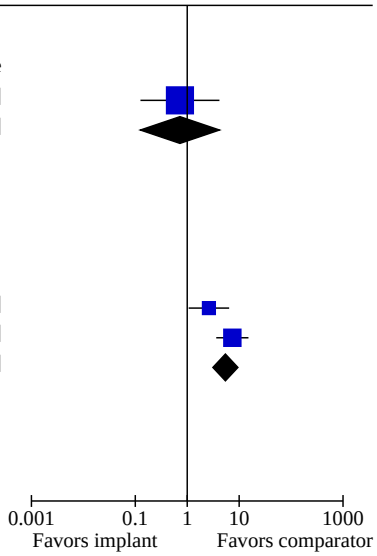


Footnotes

(1) FAi 0.18 mg, at 12 months
(2) DEX 0.7 mg, at 26 weeks, data extracted from graphical results for the implant group
(3) FAi 0.59 mg, at 24 months, eye was unit of analysis
(4) FAi 0.59 mg, at 24 months

Analysis 2.6. Comparison 2: Steroid implant vs sham procedure: ocular adverse events, Outcome 6: Proportion of eyes that underwent IOP-lowering surgery

Study or Subgroup	Implant Events	Implant Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.6.1 Sham procedure						
Lowder 2011 (1)	0	77	0	76		Not estimable
Jaffe 2019 (2)	3	87	2	42	100.0%	0.72 [0.13 , 4.17]
Subtotal (95% CI)		**164**		**118**	**100.0%**	**0.72 [0.13 , 4.17]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.36 (P = 0.72)						
2.6.2 Standard-of-care						
Pavesio 2010 (3)	14	66	6	74	41.1%	2.62 [1.07 , 6.42]
Kempen 2011 (4)	61	233	8	226	58.9%	7.40 [3.62 , 15.10]
Subtotal (95% CI)		**299**		**300**	**100.0%**	**5.43 [3.12 , 9.45]**
Total events:	75		14			
Heterogeneity: Chi² = 3.27, df = 1 (P = 0.07); I² = 69%						
Test for overall effect: Z = 5.99 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						

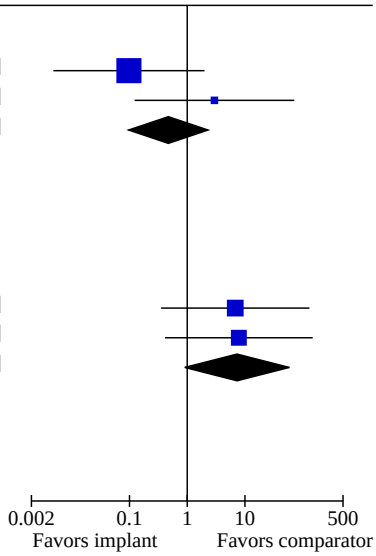


Footnotes

(1) DEX 0.7 mg, at 26 weeks
(2) FAi 0.18 mg, at 12 months
(3) FAi 0.59 mg, at 24 months
(4) FAi 0.59 mg, at 24 months, eye was unit of analysis

Analysis 2.7. Comparison 2: Steroid implant vs sham procedure: ocular adverse events, Outcome 7: Proportion of eyes with endophthalmitis

Study or Subgroup	Implant Events	Implant Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.7.1 Sham procedure						
Jaffe 2019 (1)	0	87	2	42	87.0%	0.10 [0.00 , 1.99]
Lowder 2011 (2)	1	76	0	75	13.0%	2.96 [0.12 , 71.55]
Subtotal (95% CI)		**163**		**117**	**100.0%**	**0.47 [0.10 , 2.30]**
Total events:	1		2			
Heterogeneity: Chi² = 2.33, df = 1 (P = 0.13); I² = 57%						
Test for overall effect: Z = 0.93 (P = 0.35)						
2.7.2 Standard-of-care						
Kempen 2011 (3)	3	237	0	230	51.8%	6.79 [0.35 , 130.81]
Pavesio 2010 (4)	3	66	0	74	48.2%	7.84 [0.41 , 148.94]
Subtotal (95% CI)		**303**		**304**	**100.0%**	**7.30 [0.91 , 58.72]**
Total events:	6		0			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 1.87 (P = 0.06)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						

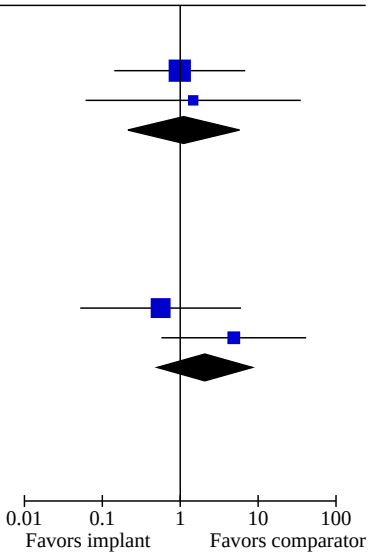


Footnotes

(1) FAi 0.18 mg, at 36 months
(2) DEX 0.7 mg, at 26 weeks
(3) FAi 0.59 mg, at 24 months, eye was unit of analysis
(4) FAi 0.59 mg, at 24 months

Analysis 2.8. Comparison 2: Steroid implant vs sham procedure: ocular adverse events, Outcome 8: Proportion of eyes with retinal tear or detachment

Study or Subgroup	Implant Events	Implant Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.8.1 Sham procedure						
Lowder 2011 (1)	2	76	2	75	75.0%	0.99 [0.14 , 6.82]
Jaffe 2019 (2)	1	87	0	42	25.0%	1.47 [0.06 , 35.24]
Subtotal (95% CI)		**163**		**117**	**100.0%**	**1.11 [0.21 , 5.75]**
Total events:	3		2			
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.90)						
2.8.2 Standard-of-care						
Pavesio 2010 (3)	1	66	2	74	65.1%	0.56 [0.05 , 6.04]
Kempen 2011 (4)	5	236	1	230	34.9%	4.87 [0.57 , 41.39]
Subtotal (95% CI)		**302**		**304**	**100.0%**	**2.07 [0.51 , 8.40]**
Total events:	6		3			
Heterogeneity: Chi² = 1.77, df = 1 (P = 0.18); I² = 44%						
Test for overall effect: Z = 1.02 (P = 0.31)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						



Footnotes
(1) DEX 0.7 mg, at 26 weeks
(2) FAi 0.18 mg, at 36 months
(3) FAi 0.59 mg, at 24 months
(4) FAi 0.59 mg, at 24 months, eye was unit of analysis

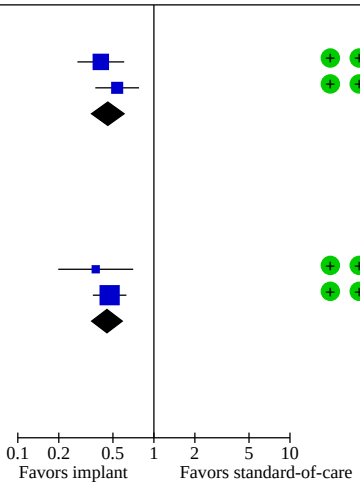
Comparison 3. Steroid implant vs standard-of-care

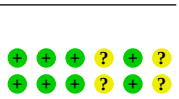
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Proportion of eyes with recurrence of uveitis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1.1 Primary efficacy time point: 24 months	2	619	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.35, 0.60]
3.1.2 Other time point: 6 months	2	619	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.35, 0.59]
3.2 Proportion of eyes with recurrence of uveitis; sensitivity analysis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.2.1 Primary efficacy time point: 24 months	2	619	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.27, 0.51]
3.2.2 Other time point: 6 months	2	619	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.35, 0.59]
3.3 Improvement in BCVA [logMAR]	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3.1 Primary efficacy time point: 24 months	2	619	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.02, 0.12]
3.3.2 Other time point: 12 months	2	619	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.06, 0.08]
3.3.3 Other time point: 6 months	2	619	Mean Difference (IV, Fixed, 95% CI)	0.06 [0.01, 0.11]
3.4 Mean difference in quality of life scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.4.1 NEI-VFQ25 (range 0 to 100); MCID: 4 to 6 points	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.4.2 SF-36 (physical component); MCID: 3 to 5 points	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.4.3 SF-36 (mental component); MCID: 3 to 5 points	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.4.4 EuroQoL (VAS, range 0 to 100); MCID: 7 points	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.4.5 EuroQoL-5D (range 0.00 to 1.00); MCID: 0.06 to 0.07 points	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3: Steroid implant vs standard-of-care, Outcome 1: Proportion of eyes with recurrence of uveitis

Study or Subgroup	Implant Events	Implant Total	Standard-of-care Events	Standard-of-care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Primary efficacy time point: 24 months						
Kempen 2011 (1)	29	245	68	234	60.6%	0.41 [0.27 , 0.61]
Pavesio 2010 (2)	23	66	48	74	39.4%	0.54 [0.37 , 0.78]
Subtotal (95% CI)		**311**		**308**	**100.0%**	**0.46 [0.35 , 0.60]**
Total events:	52		116			
Heterogeneity: Chi² = 1.05, df = 1 (P = 0.31); I² = 5%						
Test for overall effect: Z = 5.54 (P < 0.00001)						
3.1.2 Other time point: 6 months						
Pavesio 2010 (3)	10	66	30	74	21.2%	0.37 [0.20 , 0.70]
Kempen 2011 (4)	51	245	103	234	78.8%	0.47 [0.36 , 0.63]
Subtotal (95% CI)		**311**		**308**	**100.0%**	**0.45 [0.35 , 0.59]**
Total events:	61		133			
Heterogeneity: Chi² = 0.44, df = 1 (P = 0.51); I² = 0%						
Test for overall effect: Z = 6.00 (P < 0.00001)						





Footnotes

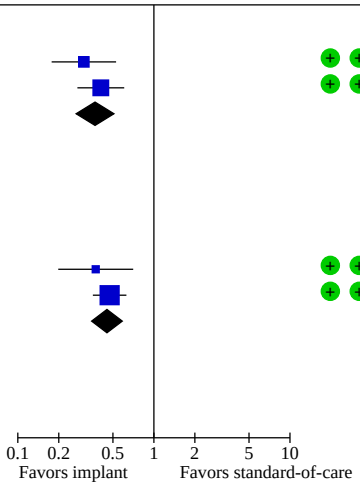
(1) FAi 0.59 mg, at 24 months, eye was unit of analysis; % of residual uveitis
(2) FAi 0.59 mg, at 24 months, primary efficacy time point
(3) FAi 0.59 mg, at 6 months; derived from Kaplan-Meyer curve
(4) FAi 0.59 mg, at 6 months; % of residual uveitis

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.2. Comparison 3: Steroid implant vs standard-of-care, Outcome 2: Proportion of eyes with recurrence of uveitis; sensitivity analysis

Study or Subgroup	Implant Events	Implant Total	Standard-of-care Events	Standard-of-care Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
3.2.1 Primary efficacy time point: 24 months												
Pavesio 2010 (1)	12	66	44	74	37.4%	0.31 [0.18 , 0.53]	+	+	+	?	+	?
Kempen 2011 (2)	29	245	68	234	62.6%	0.41 [0.27 , 0.61]	+	+	+	?	+	?
Subtotal (95% CI)		**311**		**308**	**100.0%**	**0.37 [0.27 , 0.51]**						
Total events:	41		112									
Heterogeneity: Chi² = 0.70, df = 1 (P = 0.40); I² = 0%												
Test for overall effect: Z = 6.11 (P < 0.00001)												
3.2.2 Other time point: 6 months												
Pavesio 2010 (3)	10	66	30	74	21.2%	0.37 [0.20 , 0.70]	+	+	+	?	+	?
Kempen 2011 (4)	51	245	103	234	78.8%	0.47 [0.36 , 0.63]	+	+	+	?	+	?
Subtotal (95% CI)		**311**		**308**	**100.0%**	**0.45 [0.35 , 0.59]**						
Total events:	61		133									
Heterogeneity: Chi² = 0.44, df = 1 (P = 0.51); I² = 0%												
Test for overall effect: Z = 6.00 (P < 0.00001)												



Footnotes

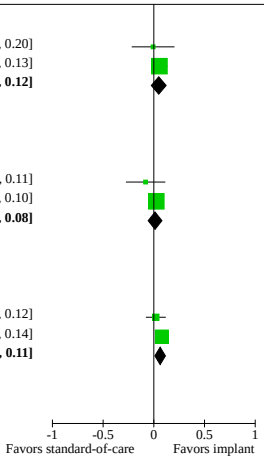
(1) FAi 0.59 mg, at 24 months, excluding inferred recurrence
(2) FAi 0.59 mg, at 24 months, eye was unit of analysis; % of residual uveitis
(3) FAi 0.59 mg, at 6 months; derived from Kaplan-Meyer curve
(4) FAi 0.59 mg, at 6 months; % of residual uveitis

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.3. Comparison 3: Steroid implant vs standard-of-care, Outcome 3: Improvement in BCVA [logMAR]

Study or Subgroup	Implant Mean [logMAR]	Implant SD [logMAR]	Implant Total	Standard-of-care Mean [logMAR]	Standard-of-care SD [logMAR]	Standard-of-care Total	Weight	Mean Difference IV, Fixed, 95% CI [logMAR]	Risk of Bias A B C D E F
3.3.1 Primary efficacy time point: 24 months									
Pavesio 2010 (1)	0.027	0.577	66	0.034	0.697	74	12.0%	-0.01 [-0.22 , 0.20]	+ + + ? + ?
Kempen 2011 (2)	0.121	0.441	245	0.065	0.431	234	88.0%	0.06 [-0.02 , 0.13]	+ + + + + +
Subtotal (95% CI)			**311**			**308**	**100.0%**	**0.05 [-0.02 , 0.12]**	
Heterogeneity: Chi² = 0.30, df = 1 (P = 0.58); I² = 0%									
Test for overall effect: Z = 1.30 (P = 0.20)									
3.3.2 Other time point: 12 months									
Pavesio 2010 (3)	-0.027	0.122	66	0.054	0.843	74	12.2%	-0.08 [-0.28 , 0.11]	+ + + ? + ?
Kempen 2011 (4)	0.092	0.432	245	0.067	0.376	234	87.8%	0.02 [-0.05 , 0.10]	+ + + + + +
Subtotal (95% CI)			**311**			**308**	**100.0%**	**0.01 [-0.06 , 0.08]**	
Heterogeneity: Chi² = 1.00, df = 1 (P = 0.32); I² = 0%									
Test for overall effect: Z = 0.35 (P = 0.73)									
3.3.3 Other time point: 6 months									
Pavesio 2010 (5)	0.13	0.3	66	0.11	0.29	74	28.1%	0.02 [-0.08 , 0.12]	+ + + ? + ?
Kempen 2011 (6)	0.118	0.335	245	0.039	0.349	234	71.9%	0.08 [0.02 , 0.14]	+ + + + + +
Subtotal (95% CI)			**311**			**308**	**100.0%**	**0.06 [0.01 , 0.11]**	
Heterogeneity: Chi² = 1.00, df = 1 (P = 0.32); I² = 0%									
Test for overall effect: Z = 2.35 (P = 0.02)									

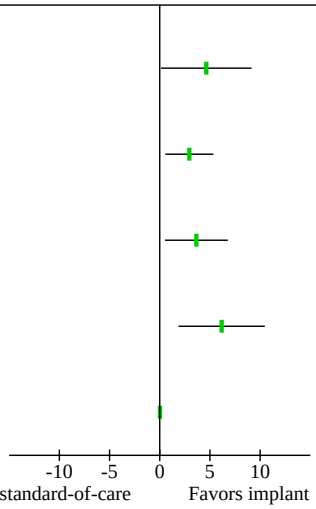


Footnotes
(1) FAi 0.59 mg, at 24 months
(2) FAi 0.59 mg, at 24 months, eye was unit of analysis
(3) FAi 0.59 mg, at 12 months
(4) FAi 0.59 mg, at 12 months, eye was unit of analysis
(5) FAi 0.59 mg, at 6 months
(6) FAi 0.59 mg, at 6 months, eye was unit of analysis

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.4. Comparison 3: Steroid implant vs standard-of-care, Outcome 4: Mean difference in quality of life scores

Study or Subgroup	Implant Mean	Implant SD	Implant Total	Standard-of-care Mean	Standard-of-care SD	Standard-of-care Total	Mean Difference IV, Fixed, 95% CI
3.4.1 NEI-VFQ25 (range 0 to 100); MCID: 4 to 6 points							
Kempen 2011 (1)	11.44	18.14	118	6.8	16.87	114	4.64 [0.13 , 9.15]
3.4.2 SF-36 (physical component); MCID: 3 to 5 points							
Kempen 2011	1.15	9.02	118	-1.8	9.61	114	2.95 [0.55 , 5.35]
3.4.3 SF-36 (mental component); MCID: 3 to 5 points							
Kempen 2011	2.55	12.06	118	-1.1	12.28	114	3.65 [0.52 , 6.78]
3.4.4 EuroQoL (VAS, range 0 to 100); MCID: 7 points							
Kempen 2011	5.29	13.9	118	-0.88	19.01	114	6.17 [1.87 , 10.47]
3.4.5 EuroQoL-5D (range 0.00 to 1.00); MCID: 0.06 to 0.07 points							
Kempen 2011	0.02	0.22	118	0	0.21	114	0.02 [-0.04 , 0.08]



Footnotes
(1) FAi 0.59 mg, at 24 months; minimal clinically important difference (MCID)

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Uveitis] explode all trees
#2 uveiti*
#3 MeSH descriptor: [Panuveitis] explode all trees
#4 Panuveitis
#5 MeSH descriptor: [Ophthalmia, Sympathetic] explode all trees
#6 (Ophthalm* near/2 Sympathetic)
#7 MeSH descriptor: [Pars Planitis] explode all trees
#8 "Pars Planitis"
#9 MeSH descriptor: [Panophthalmitis] explode all trees
#10 Panophthalmiti*
#11 MeSH descriptor: [Uveomeningoencephalitic Syndrome] explode all trees
#12 (Uveomeningoencephaliti* or "Vogt Koyanagi Harada" or VKH or fuch or "Harada disease" or "harada syndrome" or "vogt koyanagi disease")
#13 MeSH descriptor: [Behcet Syndrome] explode all trees
#14 (behcet* or "triple symptom complex")
#15 MeSH descriptor: [Iridocyclitis] explode all trees
#16 (Iridocycliti* or (Heterochromic NEXT/1 Cycliti*) or "anterior scleritis")
#17 MeSH descriptor: [Iritis] explode all trees
#18 Iriti*
#19 Choroiditis
#20 (choroiditi* or retinochoroiditi* or chorioretinitis)
#21 ((Blau* NEXT/1 syndrome) or "familial juvenile systemic granulomatosis" or "Jabs disease")
#22 ((Reiter* NEXT/1 disease) or (reiter* NEXT/1 syndrome) or "conjunctivo urethro synovial" or "urethrooculosynovial syndrome" or uroarthritis)
#23 (uveoretinitis or "uveo retinitis")
#24 vitritis*
#25 MeSH descriptor: [Retinitis] explode all trees
#26 retinitis or neuroretinitis
#27 {OR #1-#26}
#28 MeSH descriptor: [Fluocinolone Acetonide] explode all trees
#29 (fluocinolone* OR adermina OR alfabios OR alvadermo OR aplosyn OR capex OR cervicum OR cinolon OR clofeet OR "Co Fluocin" OR Cortiespec OR cortilona OR cremisona OR cynozet OR "derma-smooth/fs" OR "Derma Smooth FS" OR "derma-smoothe/fs" OR dermalar OR dermoflam OR dermoran OR dermotic OR "df 277" OR df277 OR esacinone OR Fluortriamcinolone OR flozet OR fluciderm OR Flucinar OR "flucinolone acetonide" OR flulone OR "flunolone-v" OR fluocet OR Fluocid OR "fluocinolon acetonid" OR "fluocinonide acetonide" OR fluoderm OR Fluodermo OR fluolar OR fluonid OR fluonide OR fluotrex OR fluquinol OR flurosyn OR flusonlen OR fluzon OR fusalar OR Flusolgen OR Gelidina OR iluvien OR inoderm OR jellin OR Jellisoft OR lluvien OR localyn OR luci OR medidur OR neosynalar OR "nsc 92339" OR nsc92339 OR "ot 401" OR ot401 OR otoken OR psoranide OR radiocin OR retisert OR "rs 1401 at" OR "rs 1401at" OR "rs1401 at" OR rs1401at OR supralan OR synalar OR synandone OR Synamol OR synemol OR synotic OR syntopic OR trisyn OR yutiq OR "67-73-2")
#30 MeSH descriptor: [Dexamethasone] explode all trees
#31 (Dexamethasone* OR adrecort OR adrenocot OR "aeroseb dex" OR "aeroseb-d" OR aflucoson OR aflucosone OR alfalyl OR anaflogistico OR aphtasolon OR arcodexan OR arcodexane OR artrosone OR auxiron OR azium OR bidexol OR "bisu ds" OR calonat OR cebedex OR cetadexon OR colofoam OR corsona OR corsone OR cortastat OR cortidex OR cortidexason OR cortidrona OR cortidrone OR cortisumman OR "dacortina fuerte" OR "dacortine fuerte" OR dalalone OR danasone OR "de-sone la" OR decacortin OR decadeltosona OR decadeltosone OR decaderm OR decadion OR decadran OR decadron OR decadronal OR decadrone OR decaesadril OR decagel OR decaject OR decalix OR decameth OR decamethasone OR decasone OR decaspray OR decasterolone OR decdan OR decilone OR decofluor OR dectancyl OR dekacort OR delladec OR deltafluoren OR deltafluorene OR dergramin OR deronil OR desacort OR desacortone OR desadrene OR desalark OR desameton OR desametone OR desigdron OR "dexa cortisyl" OR "dexa dabrosan" OR "dexa korti" OR "dexa scherosan" OR "dexa scherozon" OR "dexa scherozone" OR "dexa-p" OR "dexacen 4" OR dexachel OR dexacort OR dexacortal OR dexacorten OR dexacortin OR dexacortisyl OR dexadabroson OR dexadecadrol OR dexadrol OR dexagel OR dexagen OR dexahelvacort OR dexakorti OR dexalien OR dexalocal OR dexame OR dexamecortin OR dexameson OR dexamesone OR dexametason OR dexametasone OR dexameth OR dexamethason OR dexamethazon OR dexamethazone OR dexamethonium OR dexamonozon OR dexan OR dexane OR dexano OR dexapot OR dexascheroson OR dexascherozon OR dexascherozone OR dexason OR dexasone OR dexinoral OR dexionil OR dexmethsone OR dexona OR dexone OR dexpak OR dextelan OR dextenza OR dextrasone OR dexycu OR dezone OR dibasona OR doxamethasone OR esacortene OR "ex s1" OR exadion OR exadione OR firmalone OR "fluormethyl prednisolone" OR fluormethylprednisolon OR fluormethylprednisolone OR fluormone OR fluorocort OR fluorodelta OR fluoromethylprednisolone OR fortecortin OR gammacorten OR gammacortene OR grosodexon OR grosodexone OR hemady OR hexadecadiol OR hexadecadrol OR hexadiol OR hexadrol OR isnacort OR "isopto dex" OR isoptodex OR isoptomaxidex OR "lokalison f" OR loverine OR luxazone OR marvidione OR maxidex OR mediamethasone OR megacortin OR mephameson OR mephamesone OR metasolon OR metasolone OR "methazon ion" OR "methazone ion" OR methazonion OR methazonione OR

methylfluorprednisolone OR "metisone lafi" OR mexasone OR millicorten OR millicortenol OR "mk 125" OR mk125 OR mymethasone OR neoforderx OR neofordex OR nisomethasona OR novocort OR "nsc 34521" OR nsc34521 OR "oftan-dexa" OR opticorten OR opticortinol OR oradexan OR oradexon OR oradexone OR orgadrone OR ozurdex OR pidexon OR policort OR posurdex OR "predni f tablinen" OR "predni-f" OR "prednisolone f" OR prodexona OR prodexone OR sanamethasone OR santenson OR santeson OR sawasone OR solurex OR "solurex la" OR spoloven OR sterasone OR thilodexine OR triamcimetil OR vexamet OR visumetazone OR visumethazone OR "50-02-2")
#32 MeSH descriptor: [Drug Implants] explode all trees
#33 MeSH descriptor: [Drug Delivery Systems] explode all trees
#34 (Device* or implant* or shunt* or valve* or tube*)
#35 {OR #28-#34}
#36 #27 and #35

Appendix 2. MEDLINE Ovid search strategy

1. Randomized Controlled Trial.pt.
2. Controlled Clinical Trial.pt.
3. (randomized or randomised).ab,ti.
4. placebo.ab,ti.
5. drug therapy.fs.
6. randomly.ab,ti.
7. trial.ab,ti.
8. groups.ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp animals/ not humans.sh.
11. 9 not 10
12. exp Uveitis/
13. uveiti*.tw.
14. exp Panuveitis/
15. Panuveitis.tw.
16. exp Ophthalmia, Sympathetic/
17. (Ophthalm* adj2 Sympathetic).tw.
18. exp Pars Planitis/
19. Pars Planitis.tw.
20. exp Panophthalmitis/
21. Panophthalmiti*.tw.
22. exp Uveomeningoencephalitic Syndrome/
23. (Uveomeningoencephaliti* or Vogt Koyanagi Harada or VKH or fuch or Harada disease or harada syndrome or vogt koyanagi disease).tw.
24. exp Behcet Syndrome/
25. (behcet* or triple symptom complex).tw.
26. exp Iridocyclitis/
27. (Iridocycliti* or Heterochromic Cycliti* or anterior scleritis).tw.
28. exp Iritis/
29. Iriti*.tw.
30. exp Choroiditis/
31. (choroiditi* or retinochoroiditi* or chorioretinitis).tw.
32. ((Blau* adj1 syndrome) or familial juvenile systemic granulomatosis or Jabs disease).tw.
33. ((Reiter* adj1 disease) or (reiter* adj1 syndrome) or conjunctivo urethro synovial or urethrooculosynovial syndrome or uroarthritis).tw.
34. (uveoretinitis or uveo retinitis).tw.
35. vitritis*.tw.
36. exp Retinitis/
37. (retinitis or neuroretinitis).tw.
38. or/12-37
39. exp Fluocinolone Acetonide/
40. (fluocinolone* or adermina or alfabios or alvadermo or aplosyn or capex or cervicum or cinolon or clofeet or "Co Fluocin" or Cortiespec or cortilona or cremisona or cynozet or "derma-smooth/fs" or "Derma Smooth FS" or "derma-smoothe/fs" or dermalar or dermoflam or dermoran or dermotic or "df 277" or df277 or esacinone or Fluortriamcinolone or flozet or fluciderm or Flucinar or "flucinolone acetonide" or flulone or "flunolone-v" or fluocet or Fluocid or "fluocinolon acetonid" or "fluocinonide acetonide" or fluoderm or Fluodermo or fluolar or fluonid or fluonide or fluotrex or fluquinol or flurosyn or flusonlen or fluzon or fusalar or Flusolgen or Gelidina or iluvien or inoderm or jellin or Jellisoft or lluvien or localyn or luci or medidur or neosynalar or "nsc 92339" or nsc92339 or "ot 401" or ot401 or otoken or psoranide or radiocin or retisert or "rs 1401 at" or "rs 1401at" or "rs1401 at" or rs1401at or supralan or synalar or synandone or Synamol or synemol or synotic or syntopic or trisyn or yutiq or "67-73-2").tw,rn.
41. exp Dexamethasone/

42. (Dexamethasone* or adrecort or adrenocot or "aeroseb dex" or "aeroseb-d" or aflucoson or aflucosone or alfalyl or anaflogistico or aphtasolon or arcodexan or arcodexane or artrosone or auxiron or azium or bidexol or "bisu ds" or calonat or cebedex or cetadexon or colofoam or corsona or corsone or cortastat or cortidex or cortidexason or cortidrona or cortidrone or cortisumman or "dacortina fuerte" or "dacortine fuerte" or dalalone or danasone or "de-sone la" or decacortin or decadeltosona or decadeltosone or decaderm or decadion or decadran or decadron or decadronal or decadrone or decaesadril or decagel or decaject or decalix or decameth or decamethasone or decasone or decaspray or decasterolone or decdan or decilone or decofluor or dectancyl or dekacort or delladec or deltafluoren or deltafluorene or dergramin or deronil or desacort or desacortone or desadrene or desalark or desameton or desametone or desigdron or "dexa cortisyl" or "dexa dabrosan" or "dexa korti" or "dexa scherosan" or "dexa scherozon" or "dexa scherozone" or "dexa-p" or "dexacen 4" or dexachel or dexacort or dexacortal or dexacorten or dexacortin or dexacortisyl or dexadabroson or dexadecadrol or dexadrol or dexagel or dexagen or dexahelvacort or dexakorti or dexalien or dexalocal or dexame or dexamecortin or dexameson or dexamesone or dexametason or dexametasone or dexameth or dexamethason or dexamethazon or dexamethazone or dexamethonium or dexamonozon or dexan or dexane or dexano or dexapot or dexascheroson or dexascherozon or dexascherozone or dexason or dexasone or dexinoral or dexionil or dexmethsone or dexona or dexone or dexpak or dextelan or dextenza or dextrasone or dexycu or dezone or dibasona or doxamethasone or esacortene or "ex s1" or exadion or exadione or firmalone or "fluormethyl prednisolone" or fluormethylprednisolon or fluormethylprednisolone or fluormone or fluorocort or fluorodelta or fluoromethylprednisolone or fortecortin or gammacorten or gammacortene or grosodexon or grosodexone or hemady or hexadecadiol or hexadecadrol or hexadiol or hexadrol or isnacort or "isopto dex" or isoptodex or isoptomaxidex or "lokalison f" or loverine or luxazone or marvidione or maxidex or mediamethasone or megacortin or mephameson or mephamesone or metasolon or metasolone or "methazon ion" or "methazone ion" or methazonion or methazonione or methylfluorprednisolone or "metisone lafi" or mexasone or millicorten or millicortenol or "mk 125" or mk125 or mymethasone or neoforderx or neofordex or nisomethasona or novocort or "nsc 34521" or nsc34521 or "oftan-dexa" or opticorten or opticortinol or oradexan or oradexon or oradexone or orgadrone or ozurdex or pidexon or policort or posurdex or "predni f tablinen" or "predni-f" or "prednisolone f" or prodexona or prodexone or sanamethasone or santenson or santeson or sawasone or solurex or "solurex la" or spoloven or sterasone or thilodexine or triamcimetil or vexamet or visumetazone or visumethazone or "50-02-2").tw,rn.
43. exp Drug Implants/
44. exp Absorbable Implants/
45. exp Drug Delivery Systems/
46. (Device* or implant* or shunt* or valve* or tube*).tw.
47. or/39-46
48. 11 and 38 and 47
49. remove duplicates from 48

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville et al (Glanville 2006).

Appendix 3. PubMed search strategy

1. ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomised[tiab] OR randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])
2. uveiti*[tw] OR Panuveitis[tw] OR (Ophthalm*[tw] AND Sympathetic[tw]) OR Pars Planitis[tw] OR Panophthalmiti*[tw] OR Uveomeningoencephaliti*[tw] OR Vogt Koyanagi Harada[tw] OR VKH[tw] OR fuch[tw] OR Harada disease[tw] OR harada syndrome[tw] OR vogt koyanagi disease[tw] OR behcet*[tw] OR triple symptom complex[tw] OR Iridocycliti*[tw] OR Heterochromic Cycliti*[tw] OR anterior scleritis[tw] OR Iriti*[tw] OR choroiditi*[tw] OR retinochoroiditi*[tw] OR chorioretinitis[tw] OR Blau* syndrome[tw] OR familial juvenile systemic granulomatosis[tw] OR Jabs disease[tw] OR Reiter* disease[tw] OR reiter* syndrome[tw] OR conjunctivo urethro synovial[tw] OR urethrooculosynovial syndrome[tw] OR uroarthritis[tw] OR uveoretinitis[tw] OR uveo retinitis[tw] OR vitritis*[tw] OR retinitis[tw] OR neuroretinitis[tw]
3. (fluocinolone*[tw] OR adermina[tw] OR alfabios[tw] OR alvadermo[tw] OR aplosyn[tw] OR capex[tw] OR cervicum[tw] OR cinolon[tw] OR clofeet[tw] OR "Co Fluocin"[tw] OR Cortiespec[tw] OR cortilona[tw] OR cremisona[tw] OR cynozet[tw] OR "derma-smooth/fs"[tw] OR "Derma Smooth FS"[tw] OR "derma-smoothe/fs"[tw] OR dermalar[tw] OR dermoflam[tw] OR dermoran[tw] OR dermotic[tw] OR "df 277"[tw] OR df277[tw] OR esacinone[tw] OR Fluortriamcinolone[tw] OR flozet[tw] OR fluciderm[tw] OR Flucinar[tw] OR "flucinolone acetonide"[tw] OR flulone[tw] OR "flunolone-v"[tw] OR fluocet[tw] OR Fluocid[tw] OR "fluocinolon acetonid"[tw] OR "fluocinonide acetonide"[tw] OR fluoderm[tw] OR Fluodermo[tw] OR fluolar[tw] OR fluonid[tw] OR fluonide[tw] OR fluotrex[tw] OR fluquinol[tw] OR flurosyn[tw] OR flusonlen[tw] OR fluzon[tw] OR fusalar[tw] OR Flusolgen[tw] OR Gelidina[tw] OR iluvien[tw] OR inoderm[tw] OR jellin[tw] OR Jellisoft[tw] OR lluvien[tw] OR localyn[tw] OR luci[tw] OR medidur[tw] OR neosynalar[tw] OR "nsc 92339"[tw] OR nsc92339[tw] OR "ot 401"[tw] OR ot401[tw] OR otoken[tw] OR psoranide[tw] OR radiocin[tw] OR retisert[tw] OR "rs 1401 at"[tw] OR "rs 1401at"[tw] OR "rs1401 at"[tw] OR rs1401at[tw] OR supralan[tw] OR synalar[tw] OR synandone[tw] OR Synamol[tw] OR synemol[tw] OR synotic[tw] OR syntopic[tw] OR trisyn[tw] OR yutiq[tw] OR "67-73-2"[tw] OR "67-73-2"[rn])
4. (Dexamethasone*[tw] OR adrecort[tw] OR adrenocot[tw] OR "aeroseb dex"[tw] OR "aeroseb-d"[tw] OR aflucoson[tw] OR aflucosone[tw] OR alfalyl[tw] OR anaflogistico[tw] OR aphtasolon[tw] OR arcodexan[tw] OR arcodexane[tw] OR artrosone[tw] OR auxiron[tw] OR azium[tw] OR bidexol[tw] OR "bisu ds"[tw] OR calonat[tw] OR cebedex[tw] OR cetadexon[tw] OR colofoam[tw] OR corsona[tw] OR corsone[tw] OR cortastat[tw] OR cortidex[tw] OR cortidexason[tw] OR cortidrona[tw] OR cortidrone[tw] OR cortisumman[tw] OR "dacortina fuerte"[tw] OR "dacortine fuerte"[tw] OR dalalone[tw] OR danasone[tw] OR "de-sone la"[tw] OR decacortin[tw] OR decadeltosona[tw] OR decadeltosone[tw] OR decaderm[tw] OR decadion[tw] OR decadran[tw] OR decadron[tw] OR decadronal[tw] OR decadrone[tw] OR decaesadril[tw] OR decagel[tw] OR decaject[tw] OR decalix[tw] OR decameth[tw] OR decamethasone[tw]

OR decasone[tw] OR decaspray[tw] OR decasterolone[tw] OR decdan[tw] OR decilone[tw] OR decofluor[tw] OR dectancyl[tw] OR dekacort[tw] OR delladec[tw] OR deltafluoren[tw] OR deltafluorene[tw] OR dergramin[tw] OR deronil[tw] OR desacort[tw] OR desacortone[tw] OR desadrene[tw] OR desalark[tw] OR desameton[tw] OR desametone[tw] OR desigdron[tw] OR "dexa cortisyl"[tw] OR "dexa dabrosan"[tw] OR "dexa korti"[tw] OR "dexa scherosan"[tw] OR "dexa scherozon"[tw] OR "dexa scherozone"[tw] OR "dexa-p"[tw] OR "dexacen 4"[tw] OR dexachel[tw] OR dexacort[tw] OR dexacortal[tw] OR dexacorten[tw] OR dexacortin[tw] OR dexacortisyl[tw] OR dexadabroson[tw] OR dexadecadrol[tw] OR dexadrol[tw] OR dexagel[tw] OR dexagen[tw] OR dexahelvacort[tw] OR dexakorti[tw] OR dexalien[tw] OR dexalocal[tw] OR dexame[tw] OR dexamecortin[tw] OR dexameson[tw] OR dexamesone[tw] OR dexametason[tw] OR dexametasone[tw] OR dexameth[tw] OR dexamethason[tw] OR dexamethazon[tw] OR dexamethazone[tw] OR dexamethonium[tw] OR dexamonozon[tw] OR dexan[tw] OR dexane[tw] OR dexano[tw] OR dexapot[tw] OR dexascheroson[tw] OR dexascherozon[tw] OR dexascherozone[tw] OR dexason[tw] OR dexasone[tw] OR dexinoral[tw] OR dexionil[tw] OR dexmethsone[tw] OR dexona[tw] OR dexone[tw] OR dexpak[tw] OR dextelan[tw] OR dextenza[tw] OR dextrasone[tw] OR dexycu[tw] OR dezone[tw] OR dibasona[tw] OR doxamethasone[tw] OR esacortene[tw] OR "ex s1"[tw] OR exadion[tw] OR exadione[tw] OR firmalone[tw] OR "fluormethyl prednisolone"[tw] OR fluormethylprednisolon[tw] OR fluormethylprednisolone[tw] OR fluormone[tw] OR fluorocort[tw] OR fluorodelta[tw] OR fluoromethylprednisolone[tw] OR fortecortin[tw] OR gammacorten[tw] OR gammacortene[tw] OR grosodexon[tw] OR grosodexone[tw] OR hemady[tw] OR hexadecadiol[tw] OR hexadecadrol[tw] OR hexadiol[tw] OR hexadrol[tw] OR isnacort[tw] OR "isopto dex"[tw] OR isoptodex[tw] OR isoptomaxidex[tw] OR "lokalison f"[tw] OR loverine[tw] OR luxazone[tw] OR marvidione[tw] OR maxidex[tw] OR mediamethasone[tw] OR megacortin[tw] OR mephameson[tw] OR mephamesone[tw] OR metasolon[tw] OR metasolone[tw] OR "methazon ion"[tw] OR "methazone ion"[tw] OR methazonion[tw] OR methazonione[tw] OR methylfluorprednisolone[tw] OR "metisone lafi"[tw] OR mexasone[tw] OR millicorten[tw] OR millicortenol[tw] OR "mk 125"[tw] OR mk125[tw] OR mymethasone[tw] OR neoforderx[tw] OR neofordex[tw] OR nisomethasona[tw] OR novocort[tw] OR "nsc 34521"[tw] OR nsc34521[tw] OR "oftan-dexa"[tw] OR opticorten[tw] OR opticortinol[tw] OR oradexan[tw] OR oradexon[tw] OR oradexone[tw] OR orgadrone[tw] OR ozurdex[tw] OR pidexon[tw] OR policort[tw] OR posurdex[tw] OR "predni f tablinen"[tw] OR "predni-f"[tw] OR "prednisolone f"[tw] OR prodexona[tw] OR prodexone[tw] OR sanamethasone[tw] OR santenson[tw] OR santeson[tw] OR sawasone[tw] OR solurex[tw] OR "solurex la"[tw] OR spoloven[tw] OR sterasone[tw] OR thilodexine[tw] OR triamcimetil[tw] OR vexamet[tw] OR visumetazone[tw] OR visumethazone[tw] OR "50-02-2"[tw] OR "50-02-2"[rn])
5. Device*[tw] OR implant*[tw] OR shunt*[tw] OR valve*[tw] OR tube[tw] OR tubes[tw]
6. #3 OR #4 OR #5
7. #2 AND #6
8. #1 AND #7
9. MEDLINE[sb]
10. #8 NOT #9

Appendix 4. Embase.com search strategy

#1 'randomized controlled trial'/exp
#2 'randomization'/exp
#3 'double blind procedure'/exp
#4 'single blind procedure'/exp
#5 random*:ab,ti
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 'animal'/exp OR 'animal experiment'/exp
#8 'human'/exp
#9 #7 AND #8
#10 #7 NOT #9
#11 #6 NOT #10
#12 'clinical trial'/exp
#13 (clin* NEAR/3 trial*):ab,ti
#14 ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti
#15 'placebo'/exp
#16 placebo*:ab,ti
#17 random*:ab,ti
#18 'experimental design'/exp
#19 'crossover procedure'/exp
#20 'control group'/exp
#21 'latin square design'/exp
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #22 NOT #10
#24 #23 NOT #11
#25 'comparative study'/exp
#26 'evaluation'/exp
#27 'prospective study'/exp
#28 control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti

#29 #25 OR #26 OR #27 OR #28
#30 #29 NOT #10
#31 #30 NOT (#11 OR #23)
#32 #11 OR #24 OR #31
#33 'uveitis'/exp
#34 uveiti*:ab,ti
#35 'autoimmune uveitis'/exp
#36 'behcet disease'/exp
#37 behcet*:ab,ti OR 'triple symptom complex':ab,ti
#38 'blau syndrome'/exp
#39 (blau* NEXT/1 syndrome):ab,ti OR 'familial juvenile systemic granulomatosis':ab,ti OR 'jabs disease':ab,ti
#40 'choroiditis'/exp
#41 choroiditi*:ab,ti OR chorioiditi*:ab,ti
#42 'chorioretinitis'/exp
#43 retinochoroiditi*:ab,ti OR chorioretiniti*:ab,ti
#44 'vogt koyanagi syndrome'/exp
#45 uveomeningoencephaliti*:ab,ti OR 'vogt koyanagi harada':ab,ti OR vkh:ab,ti OR fuch:ab,ti OR 'harada disease':ab,ti OR 'harada syndrome':ab,ti OR 'vogt koyanagi disease':ab,ti
#46 'intermediate uveitis'/exp
#47 'pars planitis':ab,ti
#48 'iridocyclitis'/exp
#49 iridocycliti*:ab,ti OR (heterochromic NEXT/1 cycliti*):ab,ti OR 'anterior scleritis':ab,ti
#50 'iritis'/exp
#51 iriti*:ab,ti
#52 'kirisawa uveitis'/exp
#53 'reiter syndrome'/exp
#54 (reiter* NEXT/1 disease):ab,ti OR (reiter* NEXT/1 syndrome):ab,ti OR 'conjunctivo urethro synovial':ab,ti OR 'urethrooculosynovial syndrome':ab,ti OR uroarthritis:ab,ti
#55 'sympathetic ophthalmia'/exp
#56 (ophthalm* NEXT/2 sympathetic):ab,ti
#57 'uveoretinitis'/exp
#58 uveoretinitis:ab,ti OR 'uveo retinitis':ab,ti
#59 'vitritis'/exp
#60 vitritis*:ab,ti
#61 panuveitis:ab,ti
#62 panophthalmiti*:ab,ti
#63 'retinitis'/exp
#64 retinitis:ab,ti OR neuroretinitis:ab,ti
#65 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64
#66 'fluocinolone acetonide'/exp
#67 (fluocinolone* OR adermina OR alfabios OR alvadermo OR aplosyn OR capex OR cervicum OR cinolon OR clofeet OR "Co Fluocin" OR Cortiespec OR cortilona OR cremisona OR cynozet OR "derma-smooth/fs" OR "Derma Smooth FS" OR "derma-smoothe/fs" OR dermalar OR dermoflam OR dermoran OR dermotic OR "df 277" OR df277 OR esacinone OR Fluortriamcinolone OR flozet OR fluciderm OR Flucinar OR flulone OR "flunolone-v" OR fluocet OR Fluocid OR "fluocinolon acetonid" OR "fluocinonide acetonide" OR fluoderm OR Fluodermo OR fluolar OR fluonid OR fluonide OR fluotrex OR fluquinol OR flurosyn OR flusonlen OR fluzon OR fusalar OR Flusolgen OR Gelidina OR iluvien OR inoderm OR jellin OR Jellisoft OR lluvien OR localyn OR luci OR medidur OR neosynalar OR "nsc 92339" OR nsc92339 OR "ot 401" OR ot401 OR otoken OR psoranide OR radiocin OR retisert OR "rs 1401 at" OR "rs 1401at" OR "rs1401 at" OR rs1401at OR supralan OR synalar OR synandone OR Synamol OR synemol OR synotic OR syntopic OR trisyn OR yutiq OR "67-73-2"):ab,ti,rn,tn
#68 'dexamethasone'/exp
#69 (Dexamethasone* OR adrecort OR adrenocot OR "aeroseb dex" OR "aeroseb-d" OR aflucoson OR aflucosone OR alfalyl OR anaflogistico OR aphtasolon OR arcodexan OR arcodexane OR artrosone OR auxiron OR azium OR bidexol OR "bisu ds" OR calonat OR cebedex OR cetadexon OR colofoam OR corsona OR corsone OR cortastat OR cortidex OR cortidexason OR cortidrona OR cortidrone OR cortisumman OR "dacortina fuerte" OR "dacortine fuerte" OR dalalone OR danasone OR "de-sone la" OR decacortin OR decadeltosona OR decadeltosone OR decaderm OR decadion OR decadran OR decadron OR decadronal OR decadrone OR decaesadril OR decagel OR decaject OR decalix OR decameth OR decamethasone OR decasone OR decaspray OR decasterolone OR decdan OR decilone OR decofluor OR dectancyl OR dekacort OR delladec OR deltafluoren OR deltafluorene OR dergramin OR deronil OR desacort OR desacortone OR desadrene OR desalark OR desameton OR desametone OR desigdron OR "dexa cortisyl" OR "dexa dabrosan" OR "dexa korti" OR "dexa scherosan" OR "dexa scherozon" OR "dexa scherozone" OR "dexa-p" OR "dexacen 4" OR dexachel OR dexacort OR dexacortal OR dexacorten OR dexacortin OR dexacortisyl OR dexadabroson OR dexadecadrol OR dexadrol OR dexagel OR dexagen OR dexahelvacort OR dexakorti OR dexalien OR dexalocal OR dexame OR dexamecortin OR dexameson OR dexamesone OR dexametason OR dexametasone OR dexameth OR dexamethason OR dexamethazon OR dexamethazone OR dexamethonium OR dexamonozon OR dexan OR dexane OR dexano OR dexapot

OR dexascheroson OR dexascherozon OR dexascherozone OR dexason OR dexasone OR dexinoral OR dexionil OR dexmethsone OR dexona OR dexone OR dexpak OR dextelan OR dextenza OR dextrasone OR dexycu OR dezone OR dibasona OR doxamethasone OR esacortene OR "ex s1" OR exadion OR exadione OR firmalone OR "fluormethyl prednisolone" OR fluormethylprednisolon OR fluormethylprednisolone OR fluormone OR fluorocort OR fluorodelta OR fluoromethylprednisolone OR fortecortin OR gammacorten OR gammacortene OR grosodexon OR grosodexone OR hemady OR hexadecadiol OR hexadecadrol OR hexadiol OR hexadrol OR isnacort OR "isopto dex" OR isoptodex OR isoptomaxidex OR "lokalison f" OR loverine OR luxazone OR marvidione OR maxidex OR mediamethasone OR megacortin OR mephameson OR mephamesone OR metasolon OR metasolone OR "methazon ion" OR "methazone ion" OR methazonion OR methazonione OR methylfluorprednisolone OR "metisone lafi" OR mexasone OR millicorten OR millicortenol OR "mk 125" OR mk125 OR mymethasone OR neoforderx OR neofordex OR nisomethasona OR novocort OR "nsc 34521" OR nsc34521 OR "oftan-dexa" OR opticorten OR opticortinol OR oradexan OR oradexon OR oradexone OR orgadrone OR ozurdex OR pidexon OR policort OR posurdex OR "predni f tablinen" OR "predni-f" OR "prednisolone f" OR prodexona OR prodexone OR sanamethasone OR santenson OR santeson OR sawasone OR solurex OR "solurex la" OR spoloven OR sterasone OR thilodexine OR triamcimetil OR vexamet OR visumetazone OR visumethazone OR "50-02-2"):ab,ti,rn,tn
#70 'drug delivery system'/exp
#71 'drug implant'/exp
#72 'biodegradable implant'/exp
#73 device*:ab,ti OR implant*:ab,ti OR shunt*:ab,ti OR valve*:ab,ti OR tube*:ab,ti
#74 #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73
#75 #32 AND #65 AND #74

Appendix 5. LILACS search strategy

((Uveitis or Uveítis or Uveíte or MH:C11.941.879$ or Panuveitis or Panuveítis or Panuveíte or "Ophthalmia Sympathetic" or "Oftalmía Simpática" or "Oftalmia Simpática" or "Pars Planitis" or "Pars Planite" or "Panophthalmitis" or "Panoftalmitis" or "Panoftalmite" or MH:C01.252.354.900.675$ or MH:C01.539.375.354.900.675$ or MH:C01.539.375.450.900.675$ or MH:C01.703.343.900.675$ or MH:C11.294.354.900.675$ or MH:C11.294.450.900.675$ or "Uveomeningoencephalitic Syndrome" or "Síndrome Uveomeningoencefálico" or "Síndrome Uveomeningoencefálica" or MH:C10.114.843$ or MH:C10.228.228.553.900$ or MH:C20.111.258.925$ or Uveomeningoencephalitis or "Vogt Koyanagi Harada" or "Harada disease" or "harada syndrome" or "vogt koyanagi disease" or "Behcet syndrome" or "Síndrome de Behçet" or MH:C07.465.075$ or MH:C14.907.940.100$ or MH:C17.800.862.150$ or "triple symptom complex" or Iridocyclitis or Iridociclitis or Iridociclite or MH:C11.941.375.360$ or "Heterochromic Cyclitis" or MH:C11.941.160.478$ or chorioretinitis or Retinitis or Retinite or MH:C11.768.773$) AND (Fluocinolone or Fluocinolona or MH:D04.808.745.432.370$ or MH:D04.808.908.394$ or adermina or alfabios or alvadermo or aplosyn or capex or cervicum or cinolon or clofeet or "Co Fluocin" or Cortiespec or cortilona or cremisona or cynozet or "derma-smooth/fs" or "Derma Smooth FS" or "derma-smoothe/fs" or dermalar or dermoflam or dermoran or dermotic or "df 277" or df277 or esacinone or Fluortriamcinolone or flozet or fluciderm or Flucinar or "flucinolone acetonide" or flulone or "flunolone-v" or fluocet or Fluocid or "fluocinolon acetonid" or "fluocinonide acetonide" or fluoderm or Fluodermo or fluolar or fluonid or fluonide or fluotrex or fluquinol or flurosyn or flusonlen or fluzon or fusalar or Flusolgen or Gelidina or iluvien or inoderm or jellin or Jellisoft or lluvien or localyn or luci or medidur or neosynalar or "nsc 92339" or nsc92339 or "ot 401" or ot401 or otoken or psoranide or radiocin or retisert or "rs 1401 at" or "rs 1401at" or "rs1401 at" or rs1401at or supralan or synalar or synandone or Synamol or synemol or synotic or syntopic or trisyn or yutiq or "67-73-2" or Dexamethasone or Dexametasona or MH:D04.808.745.432.769.344$ or MH:D04.808.908.238$ or MH:D26.255.210.315$ or MH:D27.720.280.210.315$ or MH:E07.695.025$ or Dexamethasone or adrecort or adrenocot or "aeroseb dex" or "aeroseb-d" or aflucoson or aflucosone or alfalyl or anaflogistico or aphtasolon or arcodexan or arcodexane or artrosone or auxiron or azium or bidexol or "bisu ds" or calonat or cebedex or cetadexon or colofoam or corsona or corsone or cortastat or cortidex or cortidexason or cortidrona or cortidrone or cortisumman or "dacortina fuerte" or "dacortine fuerte" or dalalone or danasone or "de-sone la" or decacortin or decadeltosona or decadeltosone or decaderm or decadion or decadran or decadron or decadronal or decadrone or decaesadril or decagel or decaject or decalix or decameth or decamethasone or decasone or 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or "Sistemas de Liberación de Medicamentos" or "Sistemas de Liberação de Medicamentos" or MH:E02.319.300$ or Device$ or implant$ or shunt$ or valve$ or tube or tubes))

Appendix 6. *meta*Register of Controlled Trials search strategy

(uveitis OR panuveitis OR choroiditis OR pars planitis OR panophthalmitis OR uveomeningoencephalitic OR behcet OR iridocyclitis OR iritis OR retinitis) AND (fluocinolone OR dexamethasone OR retisert* OR device* OR implant* OR shunt* OR valve* OR tube*)

Appendix 7. ClinicalTrials.gov search strategy

(uveitis OR panuveitis OR choroiditis OR pars planitis OR panophthalmitis OR uveomeningoencephalitic OR behcet OR iridocyclitis OR iritis OR retinitis) AND (fluocinolone OR dexamethasone OR retisert OR device OR implant OR shunt OR valve OR tube)

Appendix 8. ICTRP search strategy

uveitis AND fluocinolone OR uveitis AND dexamethasone OR uveitis AND retisert OR uveitis AND device OR uveitis AND implant OR uveitis AND shunt OR uveitis AND valve OR uveitis AND tube OR panuveitis AND fluocinolone OR panuveitis AND dexamethasone OR panuveitis AND retisert OR panuveitis AND device OR panuveitis AND implant OR panuveitis AND shunt OR panuveitis AND valve OR panuveitis AND tube OR choroiditis AND fluocinolone OR choroiditis AND dexamethasone OR choroiditis AND retisert OR choroiditis AND device OR choroiditis AND implant OR choroiditis AND shunt OR choroiditis AND valve OR choroiditis AND tube OR pars planitis AND fluocinolone OR pars planitis AND dexamethasone OR pars planitis AND retisert OR pars planitis AND device OR pars planitis AND implant OR pars planitis AND shunt OR pars planitis AND valve OR pars planitis AND tube OR panophthalmitis AND fluocinolone OR panophthalmitis AND dexamethasone OR panophthalmitis AND retisert OR panophthalmitis AND device OR panophthalmitis AND implant OR panophthalmitis AND shunt OR panophthalmitis AND valve OR panophthalmitis AND tube

uveomeningoencephalitic AND fluocinolone OR uveomeningoencephalitic AND dexamethasone OR uveomeningoencephalitic AND retisert OR uveomeningoencephalitic AND device OR uveomeningoencephalitic AND implant OR uveomeningoencephalitic AND shunt OR uveomeningoencephalitic AND valve OR uveomeningoencephalitic AND tube OR behcet AND fluocinolone OR behcet AND dexamethasone OR behcet AND retisert OR behcet AND device OR behcet AND implant OR behcet AND shunt OR behcet AND valve OR behcet AND tube OR iridocyclitis AND fluocinolone OR iridocyclitis AND dexamethasone OR iridocyclitis AND retisert OR iridocyclitis AND device OR iridocyclitis AND implant OR iridocyclitis AND shunt OR iridocyclitis AND valve OR iridocyclitis AND tube OR iritis AND fluocinolone OR iritis AND dexamethasone OR iritis AND retisert OR iritis AND device OR iritis AND implant OR iritis AND shunt OR iritis AND valve OR iritis AND tube OR retinitis AND fluocinolone OR retinitis AND dexamethasone OR retinitis AND retisert OR retinitis AND device OR retinitis AND implant OR retinitis AND shunt OR retinitis AND valve OR retinitis AND tube

WHAT'S NEW

Date	Event	Description
2 August 2023	New citation required but conclusions have not changed	Errors in text, axis labels, and Summary of Finding tables corrected; conclusions unchanged.
2 August 2023	Amended	Errors in text, axis labels, and Summary of Finding tables corrected; conclusions unchanged.

HISTORY

Protocol first published: Issue 4, 2013
Review first published: Issue 2, 2016

Date	Event	Description
10 January 2022	New citation required and conclusions have changed	Inclusion criteria expanded, but did not affect search strategies. Two new trials identified and included for synthesis.
16 November 2021	New search has been performed	New search performed; included one new term, 'Yutiq', which is a newer equivalent to 'Retisert*'

CONTRIBUTIONS OF AUTHORS

For the update, all review authors reviewed and agreed upon the eligibility criteria, participated in study selection, data abstraction, data analysis, results interpretation, drafted portions of the review; commented critically on drafts regarding intellectual content, and approved the final version for publication.

DECLARATIONS OF INTEREST

Amit Reddy: no financial disclosures

Su-Hsun Liu: reports a grant UG1 EY020522 from the National Eye Institute, National Institutes of Health, USA; payment to institution

Christopher J Brady: No financial conflicts of interest

Pamela C Sieving: reports no financial conflicts. She is a special volunteer for the National Eye Institute, National Institutes of Health, USA: this is an unpaid position in which she performs occasional literature searches and analysis of scholarly impact for NEI staff.

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- Queen's University of Belfast, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. For the updated search, we modified the search strategies by including one term, 'Yutiq', which is a newer equivalent to 'Retisert*' used in the original search strategies.
2. To allow for evaluations of effectiveness and adverse effects of corticosteroid implants compared with 'no treatment', we also decided to include trials that used sham procedures as the comparator. We further performed separate comparisons and subgroup analyses by comparator to explore differential effects of steroid implants when compared with sham versus with standard care.
3. For this update, we also decided to use the new version of the risk of bias tool, RoB 2, to assess risk of bias in two outcomes: the proportion of recurrence of uveitis (the primary outcome) and mean changes in best corrected visual acuity (BCVA).
4. Before data extraction, we decided not to include "treatment-associated systemic adverse events" in the Summary of Finding tables because we did not expect to encounter sufficient numbers of events reported during the trial period.
5. We extended the time points for collecting relevant review outcomes to 36 months, as reported by the included trials.
6. We did not perform subgroup analysis by age, or clinical heterogeneity, as planned in the review protocol, because of the small number of trials included. We did not perform sensitivity analysis by excluding trials of high risk of bias or trials that were sponsored by industry either, due to the small number of included trials.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [adverse effects]; *Cataract; *Panuveitis; Quality of Life; *Uveitis, Intermediate

MeSH check words

Humans