NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Adalimumab and dexamethasone for treating non-infectious uveitis

Committee papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Adalimumab and dexamethasone for treating non-infectious uveitis [ID763]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pre-meeting briefing Adalimumab and dexamethasone for treating non-infectious uveitis [ID763] *(prepared before consultation on AG report)*

Contains AIC

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the companies, the consultees and their nominated clinical experts and patient experts and
- the Assessment Group (AG) report.

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the AG before the company has checked the AG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

Key issues: clinical effectiveness

- The Assessment Group stated it could not conduct indirect analyses – does committee agree with AG rationale?
- Which clinical outcomes do the committee consider to be important for decision making including outcomes assessing inflammation to the eye and structural damage to the eye?
- Trials capture short-term effects on vision (related to inflammation), but may be too short to capture long-term consequences of inadequately controlled uveitis – do the trials underestimate the long term benefits of interventions?
- Are results generalisable to NHS (unclear how many patients from UK)?
- Note that drugs in this appraisal do not entirely cover the same populations:
  - Dexamethasone: licensed for adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis
  - Adalimumab: licensed for non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid sparing, or in whom corticosteroid treatment is inappropriate).

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Key issues: Cost-effectiveness

- There is no nationally agreed treatment pathway:
  - Is committee clear on the current treatments the interventions are likely to displace?
  - What are the most appropriate comparators for adalimumab and dexamethasone? Has the most appropriate comparator been used?
  - Are adalimumab and dexamethasone direct comparators, or used at different points in the pathway?
- The choice of annual rate of blindness in the comparator group and the relative risk of blindness for dexamethasone and adalimumab impacts the ICER considerably – which rates are most appropriate?
- The proportion of patients taken off adalimumab treatment following remission and maintaining the same quality of life has the largest impact upon the ICER for adalimumab – what is the most likely proportion?
- All base cases and scenarios showed adalimumab to be >£30,000
- Current treatment is associated with substantial treatment-related morbidity. Has the model adequately captured this?

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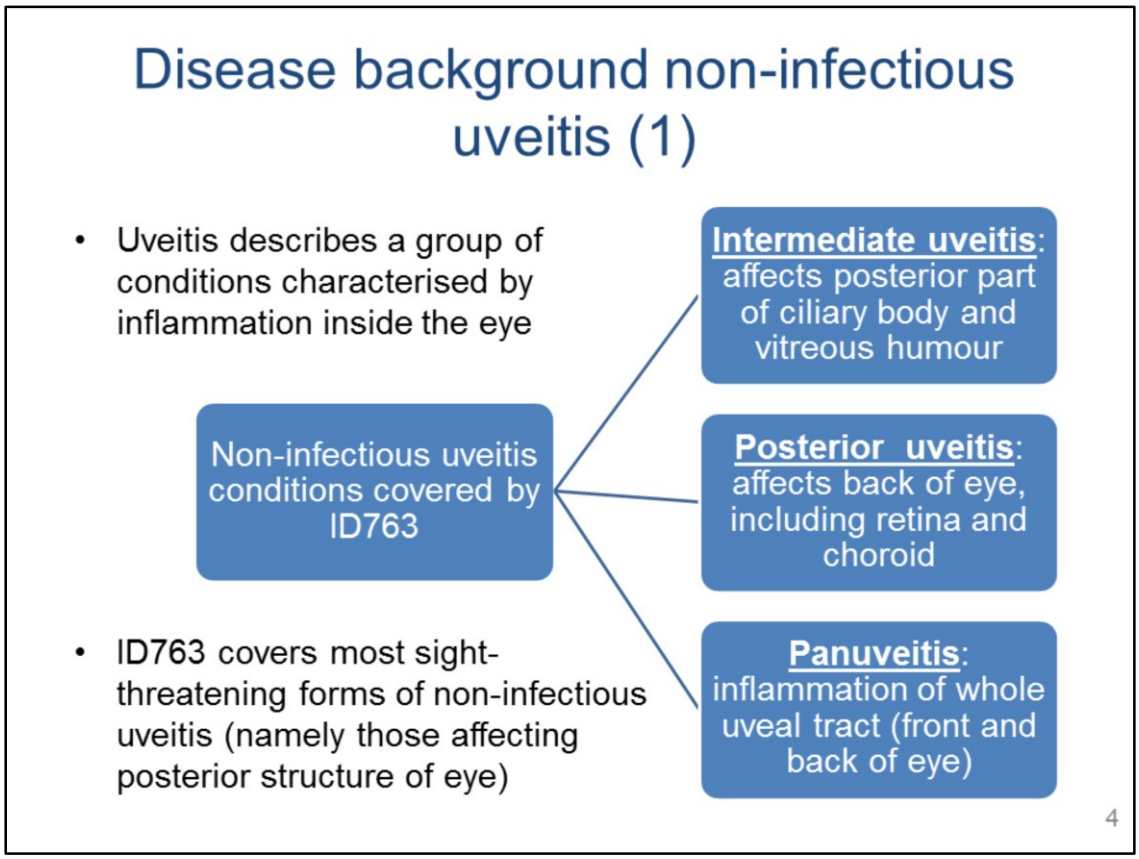
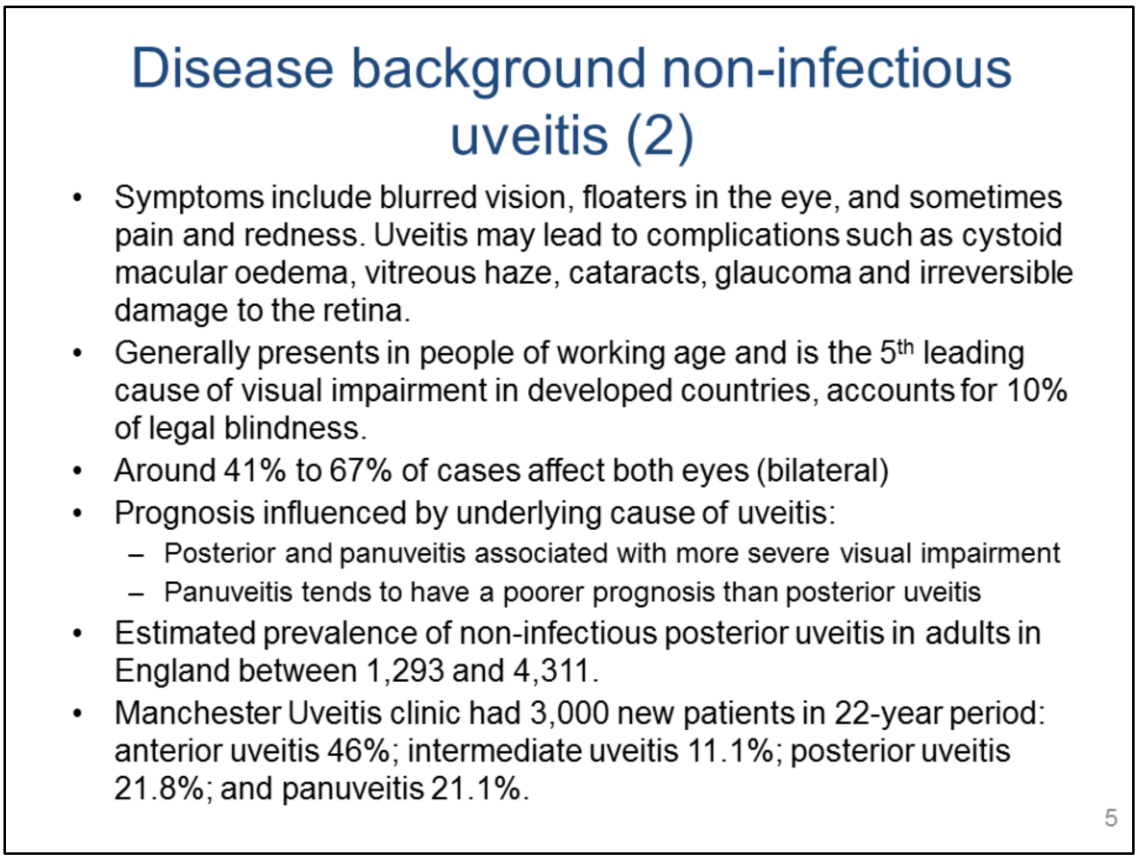


See section 3.1 (description of health problem on page 13) of Assessment Report for more details

Posterior segment uveitis refers to uveitis that affect areas of the eye posterior to the lens; it includes intermediate uveitis, posterior uveitis and panuveitis.

- Intermediate uveitis affects the middle of the eye, including the vitreous (vitritis) and peripheral retina
- posterior uveitis primarily affects the retina or choroid and may be secondarily associated with vitritis
- panuveitis affects all areas of the uveal tract.

Non-infectious uveitis may be due to an underlying inflammatory condition, an autoimmune disorder or trauma to the eye.



See section 3.1 (description of health problem on page 13) of Assessment Report for more details

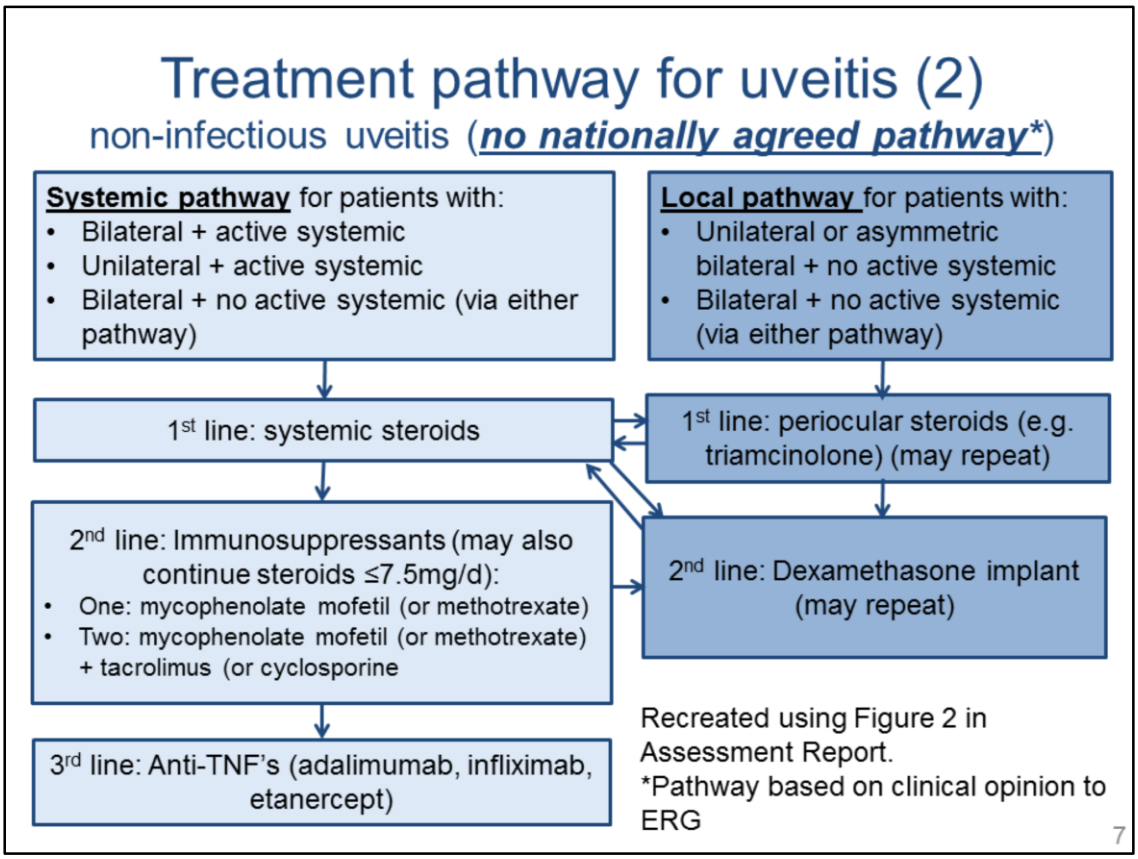
- Estimates of the proportion of bilateral cases from studies of uveitis patients in tertiary centres in the UK and Europe range from 41% to 67%.
- Clinical advisors to the AG suggested that the proportion of bilateral cases is higher for posterior segment-involving uveitis patients only, and the proportion of bilateral cases in this group was estimated to be 70-80%.
- The underlying cause of uveitis may also significantly influence the prognosis of intraocular inflammation. For example, patients with uveitis due to Behcet's disease have poorer visual outcomes even when intense treatment is initiated at early stages of the disease compared with patients with non-infectious uveitis without an associated systemic condition.
- Complications of uveitis, namely cystoid macular oedema, cataract, glaucoma or a combination of any of these significantly influence the visual morbidity.
- Prevalence is estimated to be between 3 and 10 in 100,000 people in the European Union based upon a population of 506,500,000, including people from the UK. The mid-2015 estimate for the adult population of England is 43,108,471. This results in an estimated prevalence of non-infectious posterior segment involving uveitis in adults in England of between 1293 and 4311.

Treatment pathway for uveitis (1)

- No related NICE products (Technology Appraisals, guidance or pathway)
- In clinical practice a range of unlicensed immunosuppressants and corticosteroids are used.
- Assessment group's clinical advisors suggest dexamethasone implants and adalimumab used variably in current practice depending on funding.
  - Number of patients eligible annually is uncertain.
  - Allergan estimates 589 patients eligible for dexamethasone
  - Abbvie estimates 175 patients eligible for adalimumab
- NHS England does not routinely commission infliximab and adalimumab as Anti-TNF treatment options for adult patients with Severe Refractory Uveitis.

https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/d12pa-infliximab-adalimumab-oct15.pdf 6

Note: AG did not find trials for infliximab therefore it was not included as a comparator. Infliximab is not licensed for treating uveitis.



See section 3.2 (current service provision on page 20) of the Assessment Report for more details.

National guidelines on treating non-infectious uveitis do not currently exist; however, all three clinical advisors to the AG, who practice within different regions in the UK (Birmingham, Liverpool, Sheffield), were in agreement that the description represents the general treatment pathway.

Non-infectious intermediate, posterior and panuveitis are initially treated with corticosteroids. Corticosteroids may be administered systemically (oral or parenteral), or locally via periocular or intravitreal injections or intravitreal implants. Additionally, if the front of the eye is also affected, topical corticosteroids and dilating eye drops may be offered. Systemic corticosteroids carry significant morbidity (e.g. cataract, glaucoma, diabetes, osteoporosis, weight gain, raised blood pressure) and long-term use above 7.5mg per day is not recommended.

In terms of second-line treatment, people with severe or chronic non-infectious uveitis, whose disease has not adequately responded to corticosteroid treatment, for whom corticosteroids are not appropriate, or whose uveitis recurs after tapering the corticosteroid dose, may be given immunosuppressive drugs (such as methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus and azathioprine). Immunosuppressive drugs can allow a reduction in the corticosteroid dose and associated complications. If the disease does not respond to these treatments or if they are not tolerated, especially in patients at high risk of losing their vision or those with systemic disease related to uveitis, biological TNF-alpha inhibitors may be used. The majority of these treatments are not currently licensed

Decision problem (1)

	NICE scope	Assessment group
Population	People with non-infectious, intermediate, posterior or panuveitis.	As NICE scope but considered active and inactive disease (in line with trial inclusion criteria) Note: License for dexamethasone only includes posterior
Interventions	• Adalimumab subcutaneous injection • Dexamethasone intravitreal implant	
Comparators	The interventions compared with each other where appropriate, and with: • Periocular or intravitreal corticosteroid injections • Intravitreal corticosteroid implants • Systemic corticosteroids • Systemic immunosuppressive therapies and TNF-alpha inhibitor • Intravitreal methotrexate • Best supportive care	Model assessed interventions vs current practice, using trial comparator (placebo or sham with limited immunosuppressants & corticosteroids) as: • No direct evidence comparing adalimumab with dexamethasone • Network meta analysis not appropriate due to clinical heterogeneity, lack of common comparators and outcomes

See section 4.1 (decision problem on page 26) and 4.2 (overall aims and objectives on page 27) of the Assessment Report for more details

Decision problem (2)

	NICE scope	Assessment group
Outcomes	• visual acuity (the affected eye) • visual acuity (both eyes) • mortality • adverse effects of treatment • health-related quality of life (VFQ-25 and EQ-5D)	

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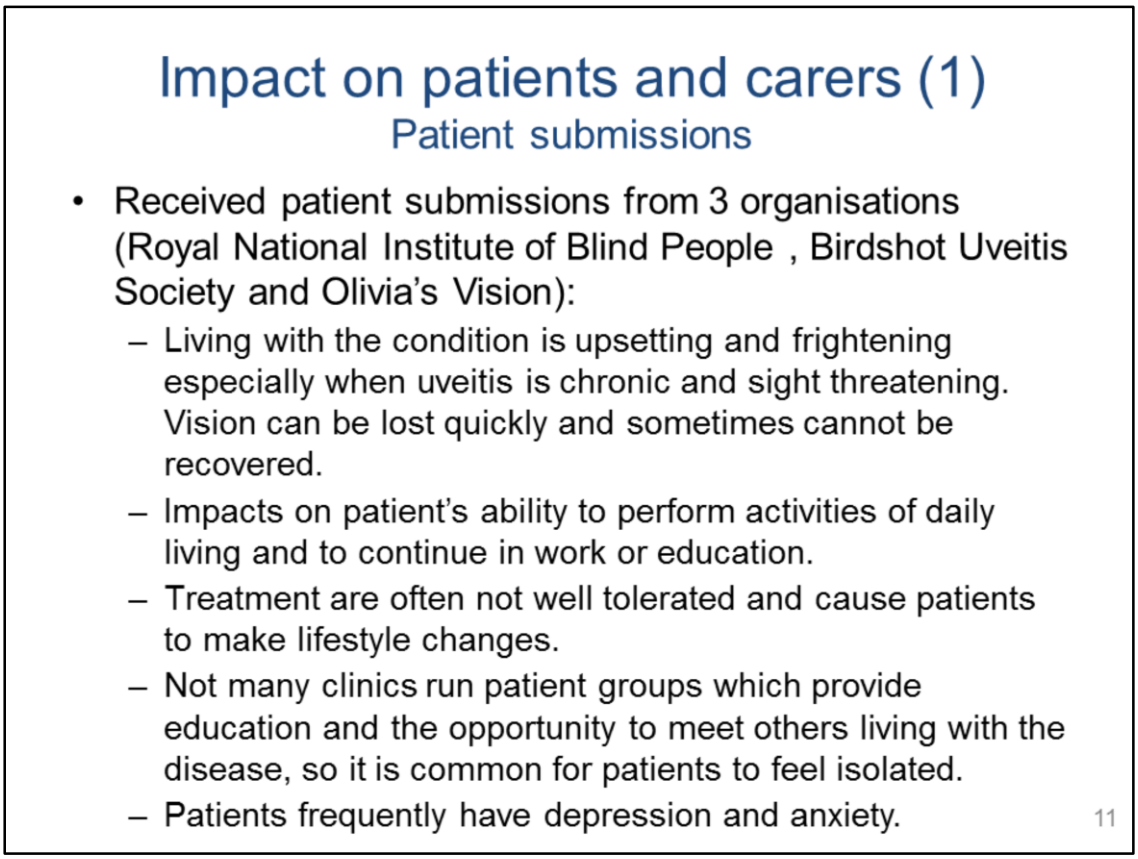
See section 4.1 (decision problem on page 26) and 4.2 (overall aims and objectives on page 27) of the Assessment Report for more details

The technologies

Dexamethasone intravitreal implant	Adalimumab subcutaneous injection
• Ozurdex (Allergan) • 0.7 mg intravitreal implant (biodegradable) in an applicator • Corticosteroid that inhibits pro-inflammatory mediators e.g. cytokines and growth factors (including vascular endothelial growth factor) • £870.00 per implant (BNF Dec 2016) • 6 monthly cost: £870 (source: AR)	• Humira (Abbvie) • 40mg/0.8ml solution for injection twice a week • Monoclonal antibody that inhibits the pro-inflammatory cytokine, tumour necrosis factor (TNF)-alpha • £704.28 per two prefilled pens/syringes or vials (BNF Dec 2016) • 6 monthly cost: £4,578 (source: AR)
Marketing authorisation	Marketing authorisation
Treatment of adult patients with inflammation of the **posterior** segment of the eye presenting as non-infectious uveitis.	Treatment of non-infectious **intermediate**, **posterior** and **panuveitis** in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid sparing, or in whom corticosteroid treatment is inappropriate. 10

See Summary of Product Characteristics (SPC) for dexamethasone (https://www.medicines.org.uk/emc/medicine/23422) and adalimumab (https://www.medicines.org.uk/emc/medicine/31860) for more details



Patients may experience sudden and temporary or progressive and permanent visual impairment

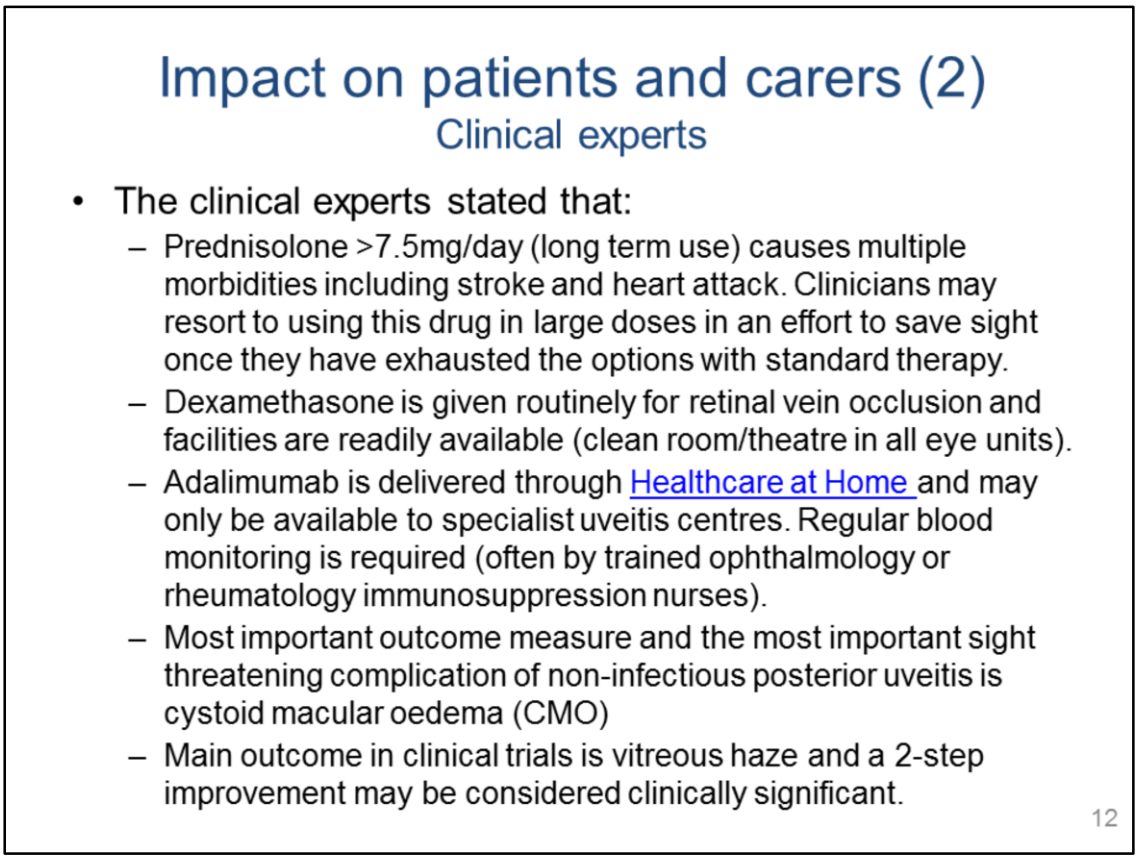
Loss of visual function can affect

- ability to work
- ability to drive
- ability to take part in leisure activities
- mental heath

Complications of uveitis (cystoid macular oedema, cataract and glaucoma) significantly influence patients' visual morbidity.

Currently available treatments (corticosteroids and immunosuppressants) are associated with substantial adverse events.

NICE received patient submission from Royal National Institute of Blind People (RNIB), Birdshot Uveitis Society (BUS) and Olivia's Vision (small charity seeks to educate patients and carers about uveitis, support patients and carers through treatment, raise funds for research into uveitis, fund and provide Fellowship training in uveitis, fund and provide training of specialist nurses charity that seeks to educate patients and carers about uveitis, support patients and carers through treatment, raise funds for research into uveitis, fund and provide Fellowship training in uveitis, fund and provide training of specialist nurses).



More information on Healthcare at Home is available here: https://www.hah.co.uk/nhs/nhs-introduction-to-healthcare-at-home/

Clinical effectiveness summary

- Assessment group carried out systematic review:
  - 16 studies retained for potential inclusion in indirect comparison
  - 13 studies related to comparators in NICE scope
  - 3 studies assessed adalimumab or dexamethasone
- Assessment report focuses on 3 trials assessing adalimumab or dexamethasone
- Non-randomised submitted for dexamethasone (by Allergen) but not adalimumab
- No direct evidence comparing adalimumab with dexamethasone.
- Not appropriate to carry out indirect comparison:
  - No common comparators (no links to network comparing adalimumab or dexamethasone)
  - Clinical heterogeneity (differences in patient characteristics e.g. active/inactive uveitis)
  - Lack of comparable outcomes in trials with common comparator

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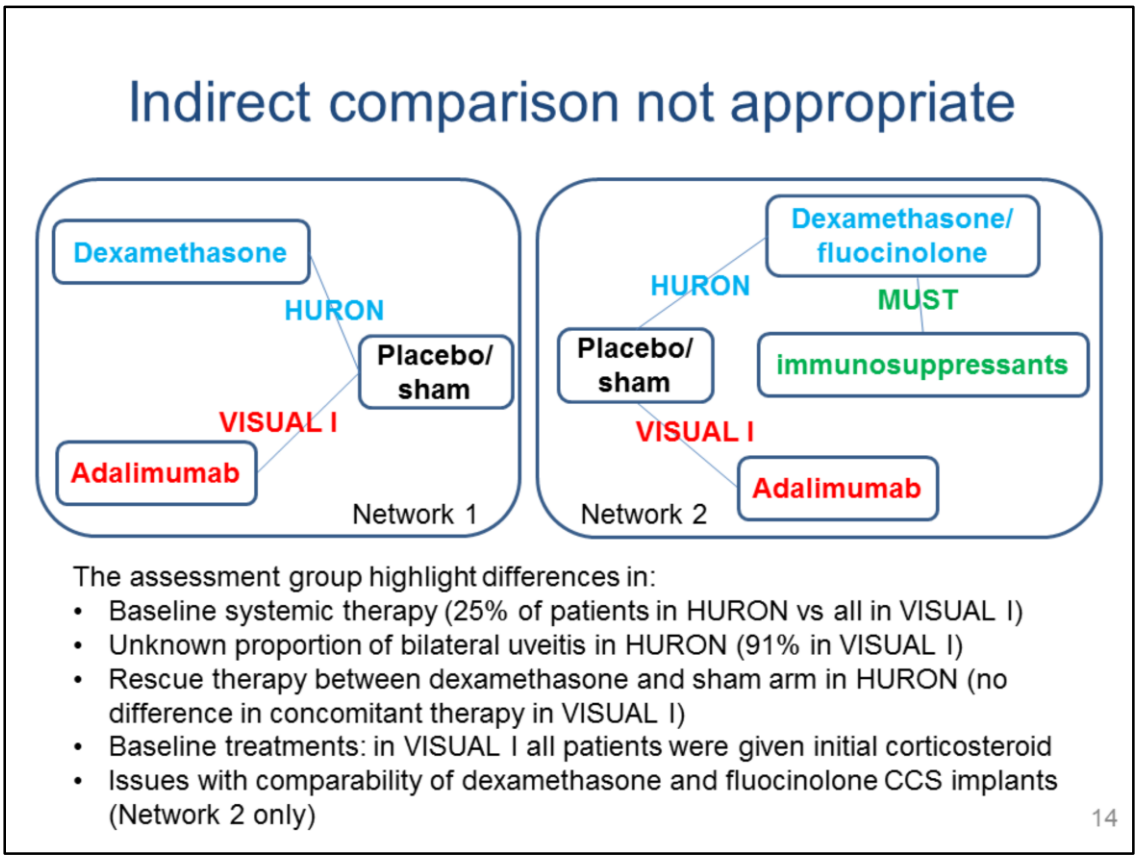
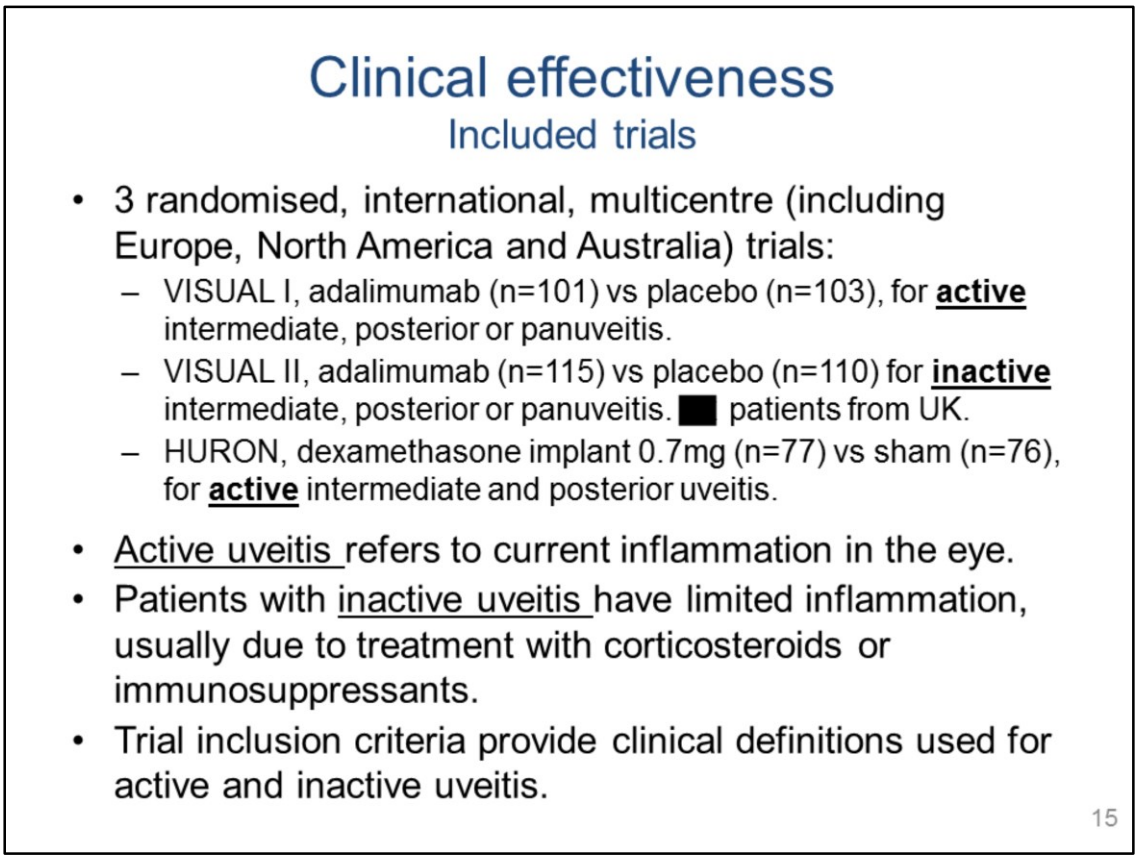
See section 5.2.3 (indirect comparison of treatments from page 79) of the Assessment Report for more details.



- **See section 5.2.3 (indirect comparison from page 79) in the Assessment Report for more details.**
- **Assessment Report Table 24 (p.81) lists all trials considered and the reasons why they were not appropriate for inclusion.**



See section 2.4 (results on page 7) and section 5 (assessment of clinical effectiveness on page 28) of the Assessment Report for more details.

VISUAL I and VISUAL II also included a sub-population of patients from Japan (n=16 patients and 32 patients, respectively); however, the Japanese patients were not included in the data reported in the study publications or company submission.

Trial characteristics

Study	Population	Inclusion criteria	F-up
VISUAL I	N=223, active non-infectious intermediate, posterior & pan uveitis	**Active** uveitis based on the manifestation of one or more of the following: VH score ≥2; AC cell grade ≥2 and/or active inflammatory chorioretinal or retinal vascular lesions whilst on high dose oral corticosteroids (10 to 60mg/day) for at least 2 weeks.	80 weeks
VISUAL II	N=229, inactive non-infectious intermediate, posterior & pan uveitis	**Inactive** uveitis characterised by VH score ≤0.5 and AC cell grade ≤0.5 with no active inflammatory chorioretinal or retinal vascular lesions (that is uveitis inactivity) whilst receiving 10 to 35mg/day oral prednisone or its equivalent to maintain an inactive state of inflammation ≥28 days before study entry.	80 weeks
HURON	N=229*, active non-infectious intermediate & posterior	**Active** intraocular inflammation based on the presence of VH score ≥1.5+. Patients unresponsive to prior corticosteroids were excluded. *0.35 and 0.7mg doses; n=153 in 0.7mg arms	26 weeks

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See section 5.2.2.1 (study characteristics page 34) of the Assessment Report for more details

In the VISUAL trials patients were considered for inclusion if control of their disease was corticosteroid-dependent, i.e. they had more than 1 uveitic flare in the past 18 months occurring within 1 month of tapering steroids.

Included studies

Baseline characteristics

Baseline characteristics	Adalimumab vs. placebo		Dexamethasone vs. sham
	VISUAL I	VISUAL II	HURON
Intermediate	22%	21%	81%
Posterior	33%	33%	19%
Panuveitis	45%	46%	None
Bilateral	91%	96%	Not reported
Prior immunosuppressant	32%	48%	25% on systemic immunosuppressant or anti-inflammatory treatment at baseline
Prior corticosteroid	All patients previously taking high dose oral corticosteroids (tapered during trial)		Not reported
Duration in months (mean, SD)	Adalimumab: 40.2 (51.3) Placebo: 51.0 (72.2)	Adalimumab: 59.5 (64.5) Placebo: 62.9 (67.7)	Dexamethasone: 50.5 (54.2) Sham: 61.2 (62.5)
All data are proportions unless otherwise stated			

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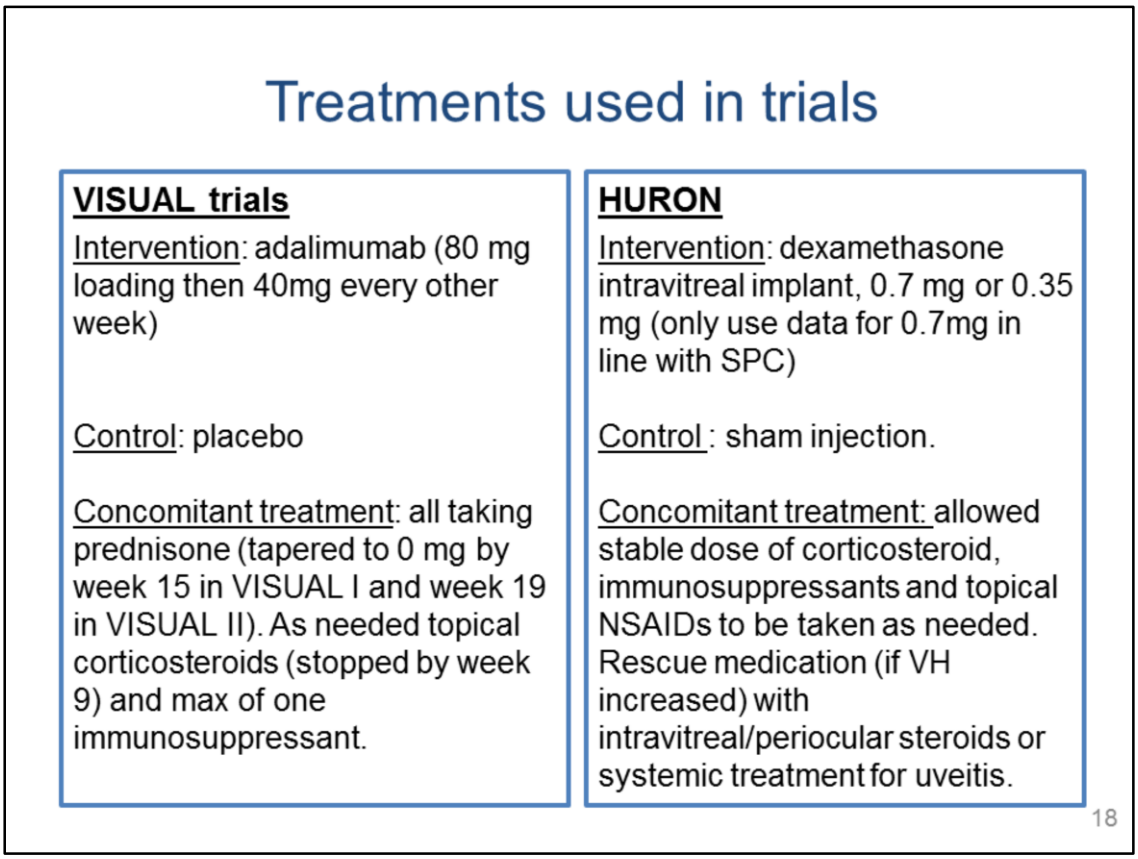
Patients included in the HURON study (mean age, 44.8 years) were slightly older than those in the VISUAL I and VISUAL II studies (mean age, 42.5 and 42.7 years, respectively). The proportion of women varied from 57% to 63%.

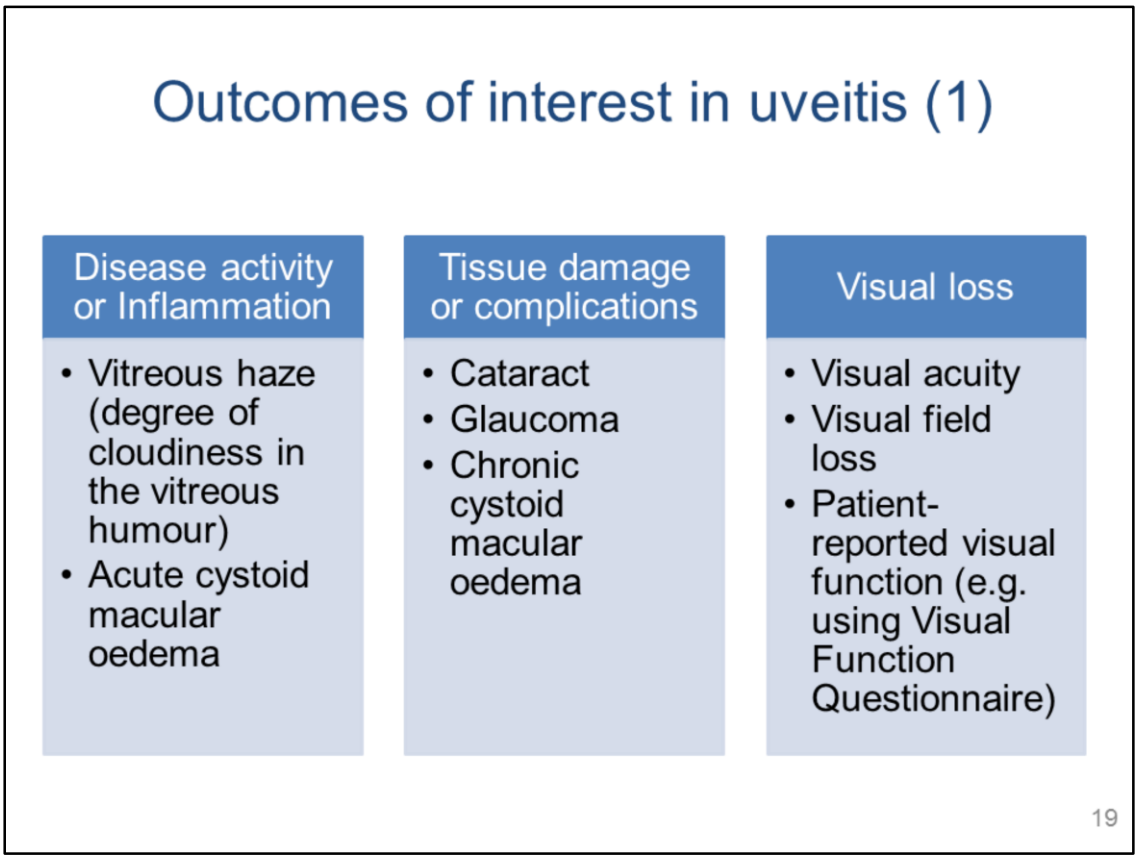
Patients have the potential to benefit more from treatment with adalimumab or dexamethasone if they have more severe uveitis, therefore the treatments are likely to be more cost-effective as the baseline disease worsens.



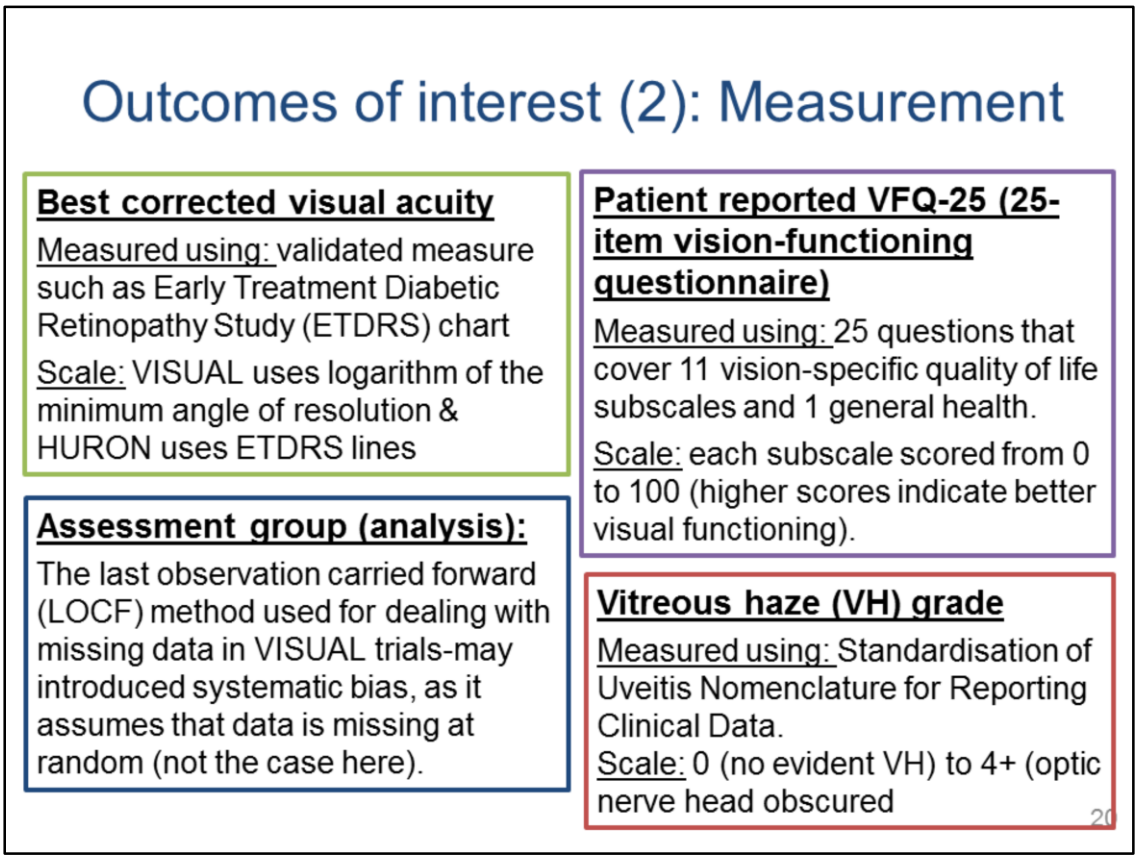
See section 5.2.2.1 (study characteristics page 39 & 40) of the Assessment Report for more details

VISUAL 1 & 2: All patients had previously received high dose oral corticosteroids (>10mg/day prednisone or its equivalent) prior to study entry and this was tapered to 0 mg by week 15 in VISUAL I and week 19 in VISUAL II. As needed topical corticosteroids (stopped by week 9) and at max of one immunosuppressant including azathioprine, cyclosporine, mycophenolate mofetil or methotrexate, at the discretion of the study investigator.

HURON: There was limited information on prior and concomitant treatments for uveitis reported for the HURON study. A quarter of patients in the relevant population (DEX 700 and sham) had received or were using systemic immunosuppressants or anti-inflammatory treatment at baseline (n=38/153, 25%). The company provided patient level data, which showed that this was generally similar across arms. However, more patients received immunosuppressant rescue therapy in the sham arm (10.5%) than the DEX 700 arm (1.3%). In HURON, new treatment or previous management requiring dose escalation with systemic corticosteroids or immunosuppressants or local (intravitreal, periocular and topical corticosteroids) was only permitted if any of these interventions was administered as rescue treatment. In general, rescue anti-inflammatory treatments were permissible, if VH score increased by ≥1 unit from week 3 to the start of week 8 and if VH =1.5+ was recorded from week 8 to 26. Other rescue medications included anticoagulants and surgical procedures on the study eye.



See section 5.2.2.3 (effectiveness results from page 51) of the Assessment Report for more details



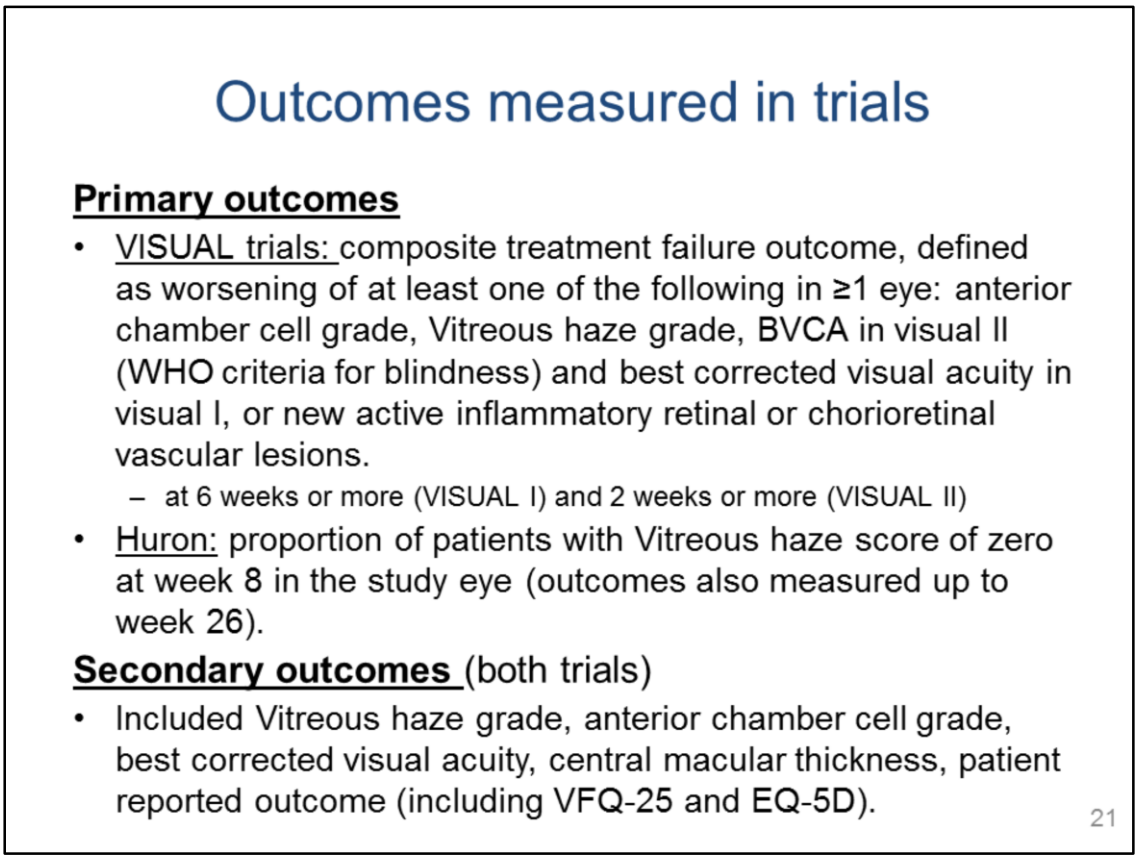
See section 5.2.2.3 (effectiveness results from page 51) of the Assessment Report for more details

The VFQ-25 is made up of 25 questions that cover 11 vision-specific quality of life subscales and 1 general health item. Condition-specific subscales covered in the tool include general vision, distance activities, near activities, vision-specific dependency, vision-specific role difficulties, vision-specific social functioning, vision-specific mental health, driving, peripheral vision and colour vision. Responses to items in each subscale are coded and scored from 0 to 100. Summary scores for each subscale are derived from an average of scores for items within the relevant subscale. A composite score is obtained by calculating the average of all the scores from the 11 vision-specific subscales. The general health item score and blank items within the instrument are excluded when calculating the composite score. Higher scores indicate better visual functioning.

VISUAL: uses EQ-5D (allows comparison with other diseases and but may not be as sensitive as VFQ-25) and VFQ-25

HURON: uses patient reported visual function from VFQ-25 (25-item vision-functioning questionnaire) and EQ-5D (US tariff) at baseline only

Vitreous haze grade in Huron proposed additional 1.5+ grade for cases that lie between the 1+ and 2+ grades. Trial inclusion criteria included VH score of at least +1.5. At baseline more patients had VH score of +1.5 to +2 (84% in dexamethasone and 87% in sham)



See section 5.2.2.1 (study characteristics page 39 & 40) of the Assessment Report for more details

Limited information on prior and concomitant treatments for uveitis was reported for the HURON study, although a quarter of patients in the relevant population (DEX 700 and sham) for this review had received or were using systemic immunosuppressants or anti-inflammatory treatment at baseline (n=38/153, 25%). The company did, however, provide patient level data, which showed that this was generally similar across arms, but that more patients received immunosuppressant rescue therapy in the sham arm (10.5%) than the DEX 700 arm (1.3%). In HURON, new treatment or previous management requiring dose escalation with systemic corticosteroids or immunosuppressants or local (intravitreal, periocular and topical corticosteroids) was only permitted if any of these interventions was administered as rescue treatment. In general, rescue anti-inflammatory treatments were permissible, if VH score increased by ≥1 unit from week 3 to the start of week 8 and if VH =1.5+ was recorded from week 8 to 26. Other rescue medications included anticoagulants and surgical procedures on the study eye.

Summary results from included trials (1)

	Adalimumab vs. placebo (95% confidence interval)		Dexamethasone vs. sham (95% CI)
Outcome	**VISUAL I**	**VISUAL II**	**HURON**
Time to treatment failure*: HR	**0.50 (0.36 to 0.70)**	**0.57 (0.39 to 0.84)**	**Not reported**
Vitreous haze=0: RR (week 8* and 26)	**Not reported**	**Not reported**	**Week 8*= 4.0 (2.0 to 7.6)** Week 26= 2.2 (1.1 to 4.1)
Mean change in visual acuity: MD	-0.07† (-0.11 to -0.02)	-0.04‡ (-0.08 to 0.01)	MD Not reported, p=0.002 at week 26
Vitreous haze (VH)**: MD	-0.27 (-0.43 to -0.11)	-0.13 (-0.28 to 0.01)	Week 8: -0.97, p<0.001 Week 26: -0.58, p<0.001
Macular oedema (change in thickness µm): MD	Not reported	Not reported	Week 8: -87.0 (-147 to -27) Week 26: -14.7 (-66 to 37)
Macular oedema (% change in thickness): MD	-11.4 (-20.9 to -1.8)	-2.3 (-8.5 to 3.8)	Not reported

Abbreviations: HR hazard ratio; RR relative risk; MD mean difference
Primary outcomes; †Change from best state reached prior to week 6 to final or early termination;
** VISUAL: Mean change in VH; HURON: Mean VH score
‡From baseline to final or early termination

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See section 5.2.2.3 (effectiveness results from page 46) of the Assessment Report for more details

Treatment failure in VISUAL trials were measured relative to baseline and treatment failure was assessed from week 2. In VISUAL I (active uveitis), treatment failure was experienced by 54.5% of patients in the ADA arm versus 78.5% in the placebo arm. The median time to treatment failure was 24 weeks (5.6 months) for ADA and 13 weeks (3 months) for placebo. In VISUAL II (inactive uveitis), treatment failure was experienced by 39% of patients in the ADA arm versus 55% in the placebo arm. The median time to treatment failure was not estimable for ADA (>18 months) because less than half of patients had experienced treatment failure, and 8.3 months for placebo

Summary results from included trials (2)

	Adalimumab vs. placebo (95% CI)		Dexamethasone vs. sham (95% CI)
Outcome	**VISUAL I**	**VISUAL II**	**HURON**
Time to macular oedema in ≤1 eye*: HR	0.70 (0.39 to 1.26)	0.75 (0.34 to 1.69)	Not reported
Visual Functioning Questionnaire-25 (VFQ-25) (composite): MD	4.20 (1.02 to 7.38)	2.12 (–0·84 to 5·08)	MD Not reported, p=0.001
VFQ-25 (>5 point improvement): MD	Not reported	Not reported	MD Not reported, p<0.05
EQ-5D: MD	0.04 (0.00 to 0.07)	0.00 (-0.03 to 0.04)	Not reported
Proportion requiring rescue medication: MD	Not reported	Not reported	MD Not reported, p=0.030

Abbreviations: HR hazard ratio; RR relative risk; MD mean difference
*Change from best state reached prior to week 6 to final or early termination
Visual Functioning Questionnaire-25

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See section 5.2.2.3 (effectiveness results from page 46) of the Assessment Report for more details

Measures of macular oedema were reported in terms of change in central macular thickness (CMT) for patients with macular oedema at baseline and time to OCT evidence of macular oedema in patients who developed the condition during the studies.

HURON also reported results in subgroups for baseline Vitreous haze (+1.5 or +2; +3 or +4) and prior treatment (prior systemic therapy and no prior systemic therapy)

Adverse events

- Adverse events measured over maximum of 80 weeks in VISUAL I (median 19 weeks in adalimumab group and 13 in placebo) and VISUAL II (median 35 weeks in adalimumab and 22 in placebo) and 26 weeks in HURON.

Adverse event	VISUAL I		VISUAL II		HURON	
	ADA %	Placebo % n=112	ADA % n=115	Placebo % n=114	Dex % n=76	Sham n=75
All events	84.7%	78.6%	91.3%	84.2%	80.3%	68.0%
All treatment related*	40.5 ADA Steroid 51.4	ADA 31.3% Steroid 47.3	ADA 55.7% Steroid 43.5	ADA 45.6% Steroid 42.1	60.5%	28.0%
Serious	13.5%	4.5%	6.1%	7.9%)	9.21%	8.0%
Serious treatment related	ADA 5.4% Steroid 1.8	ADA 1.8% Steroid 1.8	ADA 1.7% Steroid 0%	ADA 1.8% Steroid 2.6	Not reported	NR
Stopped due to adverse events	9.9%	3.6%	8.7%)	6.1%	2.6%	0%

*considered possibly treatment-related; NR, Not reported; ADA, Adalimumab; DEX, dexamethasone

See section 5.2.2.5 (safety of included interventions from page 66 and table 19 on page 69) in the Assessment Report for more details

Adalimumab: Since adalimumab affects the immune system, potential risks include infections and malignancy. Serious infections were higher for adalimumab than placebo in VISUAL I (4.5% versus 1.8%) but not VISUAL II (1.7% versus 1.8%). Malignancies and chronic renal failure each occurred in a total of 3 patients across both trials (adalimumab) versus none (placebo). Systemic AEs which were higher for adalimumab than placebo in at least one of the VISUAL studies included infections, injection site reactions, fatigue, arthralgia, myalgia, paraesthesia, hypertension and liver enzyme increases. Anti-adalimumab antibodies in patients on adalimumab occurred in 2.7% in VISUAL I and 5% in VISUAL II. There was little difference between adalimumab and placebo in rates of ocular AEs.

Dexamethasone: Risks for dexamethasone include those associated with intraocular steroids i.e. increased intraocular pressure (IOP), cataract and glaucoma, as well as infection and bleeding. In the HURON study raised IOP occurred in 25% (dexamethasone 700) versus 7% (sham), while IOP ≥25 mmHg occurred in 7.1% (dexamethasone 700) versus 1.4% (sham). Glaucoma rates were lower for dexamethasone 700 (0%) than sham (2.7%); no patients required incisional surgery for glaucoma, while 2.6% (dexamethasone 700 group) required laser iridotomies, and at any single time-point up to 23% in the dexamethasone 700 group required IOP-lowering medication (not reported for sham). Cataracts in eyes that were phakic (had a natural lens) at baseline occurred in15% (dexamethasone 700) versus 7% (sham), and cataract surgery in 1.6% (dexamethasone 700) versus 3.6% (sham). Endophthalmitis (severe eye infection) and severe uveitis worsening occurred in 1 patient each (dexamethasone 700) versus none for sham. Conjunctival haemorrhage occurred in 30% (dexamethasone 700) versus 21% (sham). No systemic adverse effects (AEs) were substantially higher for dexamethasone than sham.

Non-randomised studies

- No non-randomised studies presented for adalimumab.

Allergan submitted review of non-randomised evidence for dexamethasone:

- Provides some data on repeat implants, implants in both eyes and corticosteroid reduction (not assessed in HURON)
- 11 non-randomised, non-comparative studies
  - 3 studies reported improvements in best corrected visual acuity at 12 months in patients who received between 1 and 4 implants
  - 2 studies reported significant improvements in central retinal thickness (one study at 12 months, one study at 3 months but not 6 months) in patients having a mix of single or multiple implants
  - 1 study reported significant improvement in best corrected visual acuity at 1 month after second implant but then decreased
  - 3 studies reported a reduction in systemic, local or corticosteroid treatment (range 25% to 78%) following a single implant

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See section 5.2.2.4 (Effectiveness data from non-randomised studies of dexamethasone from page 64) of the Assessment Report for more details.

AG notes on outcome measures (1)

- Visual acuity in patients with uveitis may reflect degree of intraocular inflammation and extent of damage in the eye
  - inflammation may vary over short time periods (days or weeks)
  - damage may accrue slowly (months or years) and usually irreversible (with the exception of cataract and acute cystoid macular oedema).
- Trials capture short-term effects on vision (related to inflammation), but may be too short to capture long-term consequences of inadequately controlled uveitis
  - may lead to systematic underestimates of treatment effects.
- Markers of structural damage to the eye e.g. macular oedema (swelling of the retina), cataract and glaucoma, are important because they are mechanisms by which uveitis patients lose vision, and are objective.
  - may not be good markers of whether treatment reduces inflammation because structural damage may not resolve when inflammation treated.

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AG notes on outcome measures (2)

Clinical experts to assessment group suggest:

- proportion of patients who remain on adalimumab likely to be underestimated in VISUAL trials because of strict criteria for treatment failure
- for 'inactive' group, adalimumab more likely to be used in patients who have to discontinue existing immunosuppressants (ineffective or not tolerated) but no clinical data for this group
- no RCT evidence to assess comparative effectiveness or safety of more than one dexamethasone implant, either in both eyes or consecutively
- adalimumab and dexamethasone likely to be provided alongside other treatment options in practice (unclear if relative treatment effect would stay same if more concomitant therapy added to both arms).

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If more people were to remain on treatment, the additional group of patients on treatment would incur the same costs as those who remain on treatment in the VISUAL trial, whilst the effectiveness of adalimumab is likely to be reduced in these patients who were considered to have failed treatment in the trial, hence, the ICER would increase for these patients.

Key issues: clinical effectiveness

- The Assessment Group stated it could not conduct indirect analyses – does committee agree with AG rationale?
- Which clinical outcomes do the committee consider to be important for decision making including outcomes assessing inflammation to the eye and structural damage to the eye?
- Trials capture short-term effects on vision (related to inflammation), but may be too short to capture long-term consequences of inadequately controlled uveitis – do the trials underestimate the long term benefits of interventions?
- Are results generalisable to NHS (unclear how many patients from UK)?
- Note that drugs in this appraisal do not entirely cover the same populations:
  - Dexamethasone: licensed for adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis
  - Adalimumab: licensed for non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid sparing, or in whom corticosteroid treatment is inappropriate).

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Cost-effectiveness model
summary

- No company models submitted
- AG developed Markov model to assess cost effectiveness of:
  - dexamethasone compared with clinical practice (HURON)
  - adalimumab compared with clinical practice (VISUAL I & II).
- Dexamethasone and adalimumab not compared directly as often used in different patient scenarios and with varying indications. Also insufficient trial evidence.
- Adalimumab assessed separately for patients with active and inactive uveitis, dexamethasone assessed only for patients with active uveitis.
- Treatment effectiveness from quality of life data from included trials (VISUAL I, VISUAL II and HURON).
- Rate of blindness in comparator group and relative risk of blindness in intervention groups has big impact on incremental cost effectiveness (ICER)-assess in exploratory analyses.

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See company submission's and section 6 (assessment of cost effectiveness from page 94) in the Assessment Report for more details

AbbVie provide no discussion of cost-effectiveness, and present a budget impact estimate based on the acquisition costs of adalimumab only.

Allergan argue that dexamethasone has been recommended by NICE for the treatment of macular oedema secondary to retinal vein occlusion and that the costs per patient associated with dexamethasone are comparable, the incremental gains in visual acuity are greater in posterior segment uveitis based upon the trial data from the individual trials. The AG stated that this argument fails to consider the incremental (rather than absolute) cost of dexamethasone treatment compared with current treatment. Allergan also submitted a budget impact model, which takes into account the costs of treatment and monitoring, but not of treating events associated with uveitis or adverse events associated with treatment.

Cost effectiveness studies

- 2 economic evaluations from USA identified by Assessment Group's literature review.
  - Padula et al (2011)-conference abstract
  - Sugar et al (2014)-full text paper
- Studies did not assess adalimumab or dexamethasone
- One of the economic analyses was based on a semi-Markov model, whilst the other extrapolated cost and HRQoL data collected during the MUST trial
- Limitations of Sugar et al (2014) include:
  - poor reporting of some of the methods, validation and uncertainty analysis;
  - not taking into account adverse events
  - 3 year time horizon may not capture all impacts of treatments

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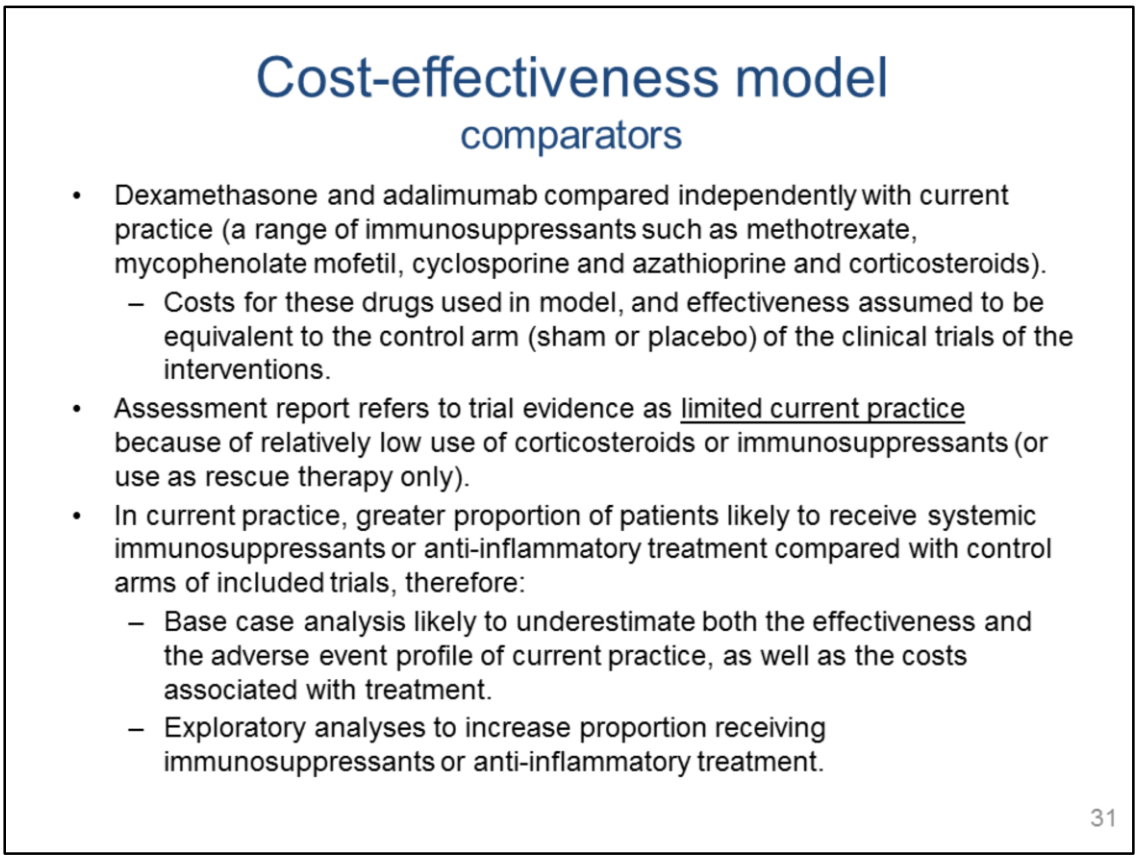
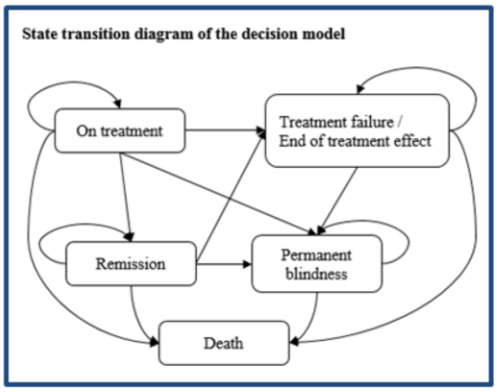
See section 6.1 (systematic review of existing cost-effectiveness studies from page 94) in the Assessment Report for more details



See page 102 (comparators) in the Assessment Report for more details

The AG noted that in clinical practice a greater proportion of patients being treated with adalimumab and dexamethasone are also likely to receive concomitant treatment.

Model structure



Source: Figure 7 in AG Report

Patients receiving dexamethasone: assumed to have active disease
Patients receiving adalimumab: active and inactive (assessed separately)

- AG developed Markov model with 5 health states
- For dexamethasone, treatment is one implant (effective 6 months)
- No indirect comparison of dexamethasone with adalimumab as trials not similar enough to be pooled
- Base case assumes no one in remission (exploratory analyses)
- During treatment HRQoL (VFQ-25 or EQ-5D) can improve with treatment effect or lower adverse events
- Lifetime time horizon, 2 week cycles and discounted at 3.5%

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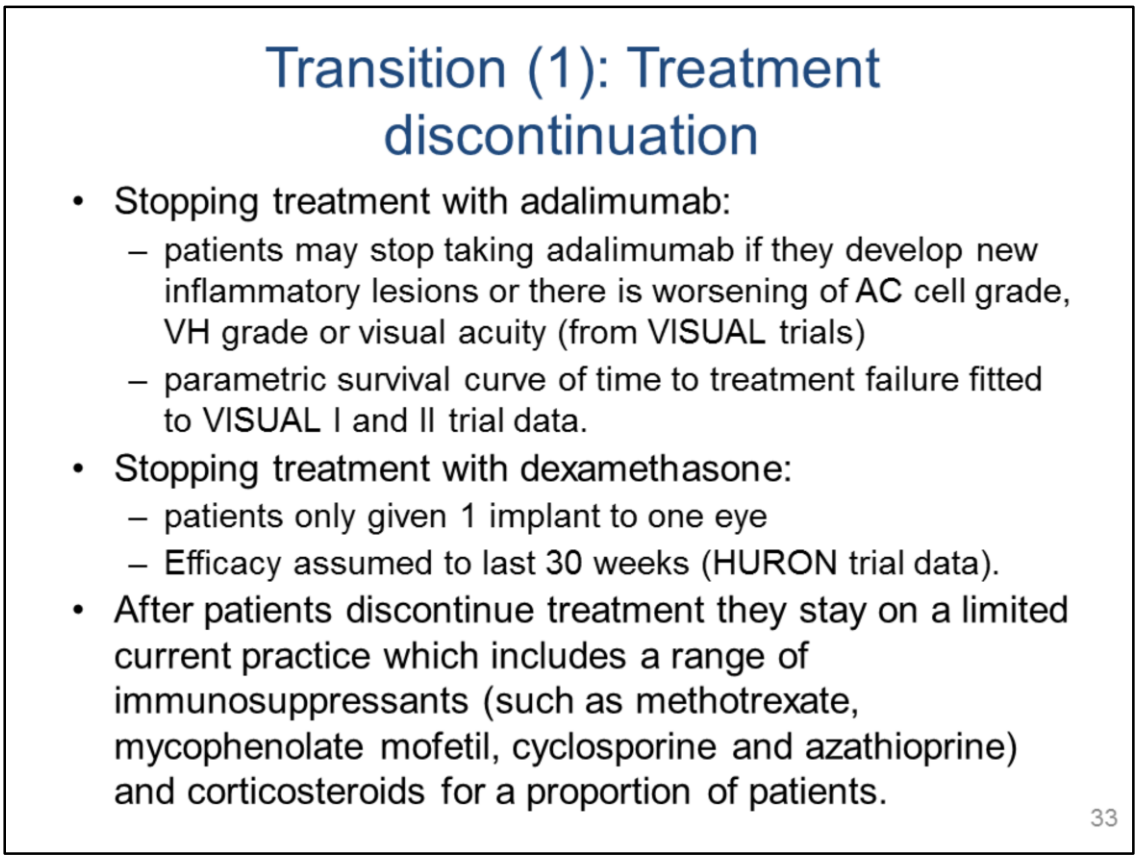
See section 6.2.1.2 (model structure from page 105) in the Assessment Report for more details

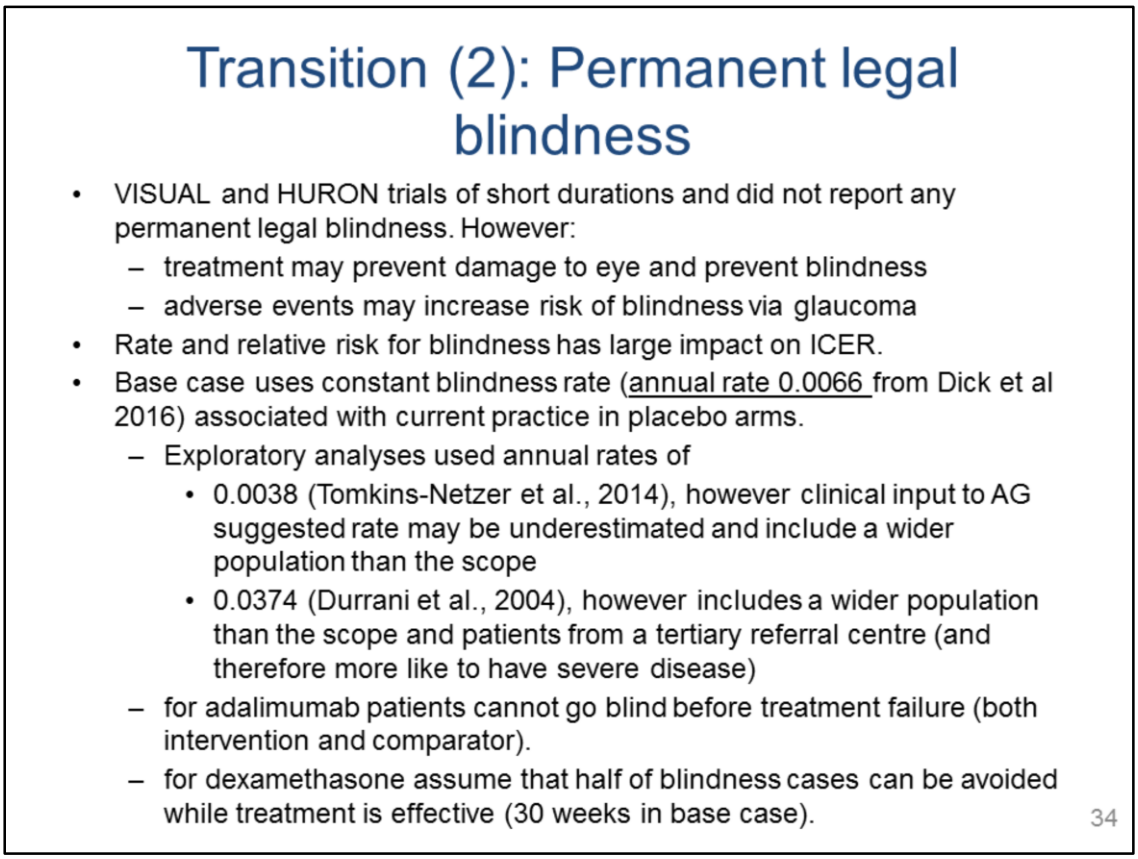
An analysis was undertaken to explore the cost-effectiveness of dexamethasone use in one eye in patients with unilateral disease and bilateral disease as separate subgroups; the trial did not provide data separately for these groups and hence it is considered to be exploratory. The AG stated that it was not possible to explore additional subgroups because of a lack of evidence.



See section 6.2.1.3 (estimation of model parameters from page 106) in the Assessment Report for more details

Treatment discontinuation was modelled using parametric curves fitted to Kaplan-Meier curves for time to treatment failure from the trials. The Kaplan-Meier curves for time to treatment failure included in the VISUAL I and II CSRs were digitised and IPD reconstructed using the methods described by Guyot *et al.* A number of parametric curves were fitted to the data.

The AG assumed that the treatments were only effective whilst they were being given. Therefore, patients who are no longer being treated with adalimumab, and patients who received the dexamethasone implant more than 6 months ago, will accrue no additional health gains.

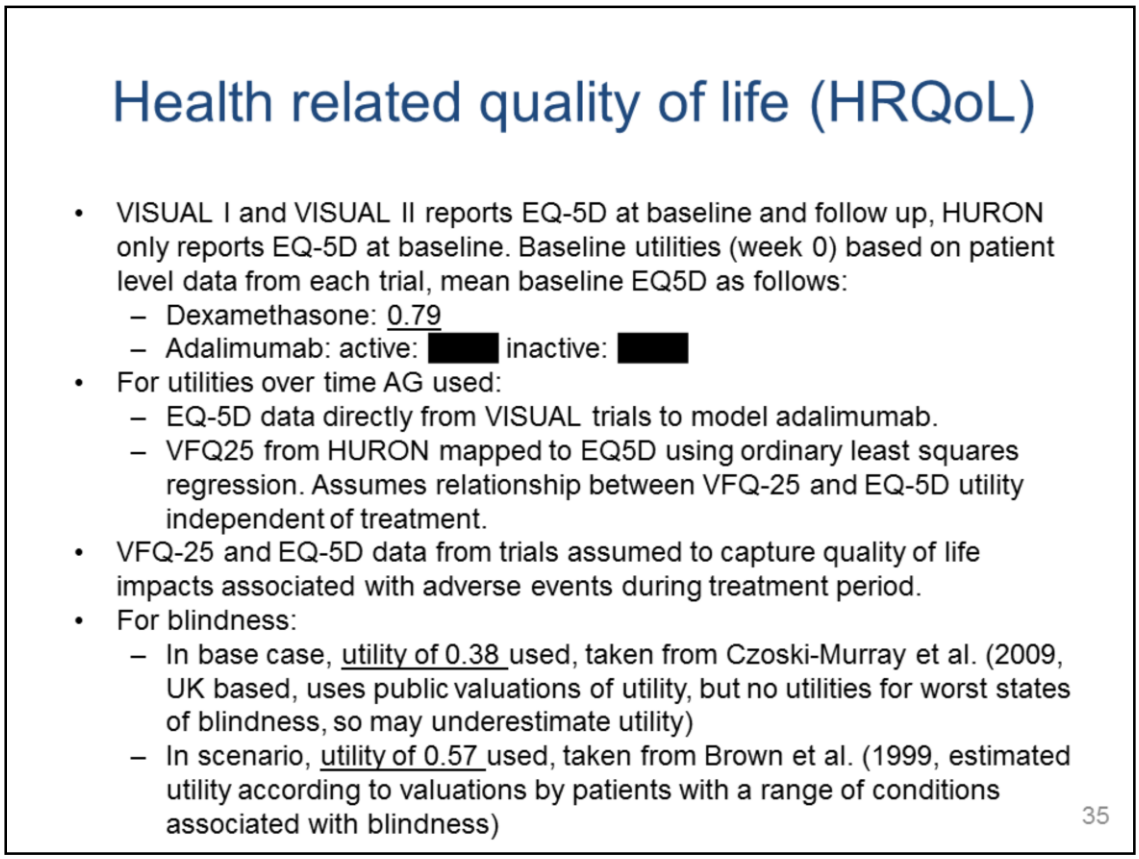


See section 6.2.1.3 (estimation of model parameters from page 109) in the Assessment Report for more details

Base case uses blindness data from Dick et al (2016), a retrospective analysis of insurance claims data in 1,769 patients with posterior segment, non-infectious uveitis.

Assessment group define blindness as a BCVA of 20/200 or less in the better-seeing eye, according to the UK definition of legal blindness. In order to model the impact of treatment with adalimumab upon the rate of blindness, given the strict criteria for treatment failure within the VISUAL trials, it was assumed that patients could not go blind before treatment failure. This was assumed both for the intervention and the comparator. The rate of blindness following treatment failure was then approximated so that the rate of blindness at each cycle in the placebo group was equivalent to the estimate from Dick *et al* (2016) The AG stated it was not clinically reasonable that a dexamethasone implant would prevent either all or no cases of blindness during treatment. As there was no evidence around this parameter, the AG sampled from a uniform distribution between 0 and 1 within the PSA and used the mean of this distribution (0.5) for the deterministic analysis. Therefore, the AG assumed that half of the cases of blindness in this group would be avoided for the period in which the treatment effect is applied (30 weeks in the base case). The AG assumed that patients in the comparator group would have the same blindness rate as in the general population.

The AG heard from clinicians that around 20%-30% of patients with uveitis have disease that remains unilateral and that patients treated with dexamethasone are more likely to have disease that is unilateral. The blindness rate for people with bilateral disease was adjusted by dividing the rate by the proportion of people with bilateral disease in the general population. The incidence of blindness in each analysis was adjusted by multiplying the rate of blindness for people with bilateral disease by the proportion of patients with bilateral disease in each population.



See section 6.2.1.3 (estimation of model parameters from page 112) in the Assessment Report for more details. See AG report Figure 17, Figure 18 and Figure 19 for predicted mean utility values over time, excluding any adjustments for blindness, for dexamethasone compared with LCP(H) for people with active disease, adalimumab compared with LCP(VI) for people with active disease, and adalimumab compared with LCP(VII) for people with inactive disease, respectively.

The AG noted that in HURON baseline utilities and visual acuity were substantially different between the sham and the dexamethasone arms (visual acuity was 71.3 for the sham arm and 63.7 for the DEX 700 arm). However clinical advisors to the AG agreed it was plausible that the differences at baseline were due to random variation. The AG explored the impact of changing the baseline utility in the univariate sensitivity analysis; however, this analysis assumed that the relative treatment effect remained the same. The AG stated this is unlikely to be the case for subgroups with differing baseline utilities such as patients with unilateral or bilateral uveitis, but there is no evidence from the trials which would enable a robust subgroup analysis.

When estimating utility over time, the AG used VFQ-25 data from each follow-up point within the HURON trial (weeks 0, 8, 16, 26) and EQ-5D data from each follow-up point of the VISUAL trials (weeks 0, 1, 4, 6, 8, 12, 16, 20, 24, 27, 32, then every four weeks until week 80) to estimate the change in utility for each treatment group over the time period of the trials. The AG adjusted these according to the average baseline utilities but maintained the change from baseline in each arm.

For adalimumab, for patients who discontinued treatment because of treatment failure, the AG assumed that utility returned to the baseline utility score, adjusted for any reduction in utility associated with age. For patients who received adalimumab beyond the duration of the trial (80 weeks), the AG assumed that their utility remained constant after the last follow-up point until treatment discontinuation. This utility is based on the mean of the last six months of data (see AG report Figures 18 and 19).

For dexamethasone, the AG assumed that the utility of patients would drop to that of its comparator after the duration of the treatment effect. In the base case, the treatment effect was assumed to be 30 weeks (4 weeks longer than the trial period). Within the sensitivity analyses, the AG assumed the utility decreased to the baseline utility score over varying time periods.

Treatment costs (1)

- Cost of treatment with immunosuppressants calculated separately for each as a weighted average of myophenolate mofetil, methotrexate, cyclosporine and azathioprine, based on usage in relevant trial.
- Cost of treatment with corticosteroids based on systemic prednisolone
- In trials, corticosteroid and other medications use similar. However, HURON reported an imbalance in rescue therapy:
  - 22.1% dexamethasone (1.3% immunosuppressant, 20.7% corticosteroid)
  - 38.2% sham (10.5% immunosuppressant, 27.7% corticosteroid)
- As corticosteroids usage more similar, and as they are relatively inexpensive, the AG modelled the costs of additional immunosuppressants only (and not additional corticosteroids).

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See section 6.2.1.3 (estimation of model parameters from page 117 and table 34 on page 119) in the Assessment Report for more details

Treatment costs (2)

Category	Drug	Dose	6-monthly cost (BNF)
Intervention	Adalimumab	40 mg every 2 weeks	£4,578
	Dexamethasone	One 0.7 mg implant	£870
Immuno-suppressant	Mycophenolate mofetil	1g twice daily	£136
	Methotrexate	15 mg weekly	£16
	Cyclosporine	2 mg per kg twice daily	£985
	Azathioprine	1 mg per kg daily	£27
Corticosteroid with concomitant treatment	Systemic prednisolone	prednisolone 7.5 mg daily	£12
	Adcal D3	20mg daily	£47.58
	Omeprazole	20mg daily	£15.25

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Source: AR Table 34 and 37 (p118 and 123)

See section 6.2.1.3 (estimation of model parameters from page 117 and table 34 on page 118) in the Assessment Report for more details

Adverse event costs (1)

- Trial data used to calculate additional costs associated with adverse events so only need to include events that have substantial cost:
  - clinical experts advised assessment group these would be cataracts, raised intra ocular pressure, glaucoma, serious infections, hypertension, fractures and diabetes.
- Incidence of diabetes and fractures assumed to be similar in the treatment and comparator arms and were included in exploratory analysis only (i.e. greater corticosteroid use in the comparator arm).

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See section 6.2.1.3 (estimation of model parameters from page 119 and table 36 on page 120) in the Assessment Report for more details

Adverse event costs (2)

Adverse event	Resource use	Cost	Frequency	Source
Cataract	Cataract surgery	£852.40	One off	NHS RC 2014-15
Raised intra ocular pressure	Two doses of bimatoprost	£23.42	One off	BNF, 2016
Glaucoma	Glaucoma surgery	£581.25	One off	NHS RC 2014-15
Serious infection	Hospitalisation	£5,940.50	One off	NHS RC 2014-15
Hypertension	Anti-hypertensive prescription	£7.04	One off	Breeze et al.
Fracture	Hospitalisations, accident and emergency visits, referrals, prescriptions and GP contacts	£2,116.17 to £6,022.62*	One off	Davis et al. 2016
Diabetes	Annual diabetes treatment and hospitalisation for complications of diabetes	£1,521.46	Annual	UKPDS study† (Alva et al. 2015) Breeze et al.

*depending on age and gender, †largest study of the costs of diabetes and complications in the UK

See section 6.2.1.3 (estimation of model parameters from page 119 and table 36 on page 120) in the Assessment Report for more details

The cost of fracture was based upon evidence from a HTA monograph by Davis *et al*. and includes hospitalisations, Accident and Emergency (A&E) visits, referrals, prescriptions and GP contacts. The cost of diabetes was based upon the annual hospitalisation costs from the UKPDS study, which is the largest study of the costs of diabetes and its complications in the UK.

Adverse event costs (3): Blindness

- Literature search for cost data limited from 2006 and most recent good quality evidence associated with costs of blindness from HTA of treatment for age related macular degeneration (Colquitt et al 2008)

Resource use	Patients	Cost	Source
Blind registration*	95%	£146	Meads et al. 2003
Low vision aids*	33%	£191	Meads et al. 2003
Low vision rehabilitation*	11%	£329	Meads et al. 2003
Depression	39%	£2,378	McCrone et al. 2008
Hip replacement	5%	£4,086	NHS Reference costs 2014-2015
Community care	6%	£281	PSSRU 2015, social care for older people
Residential care†	30%	£21,732	PSSRU 2015, private residential care
Annual total		**£7,659**	
Transition		**£237**	

Key: *, one-off; †, 30% of residents pay themselves.
Source: AR Table 35 and 36 (p120)

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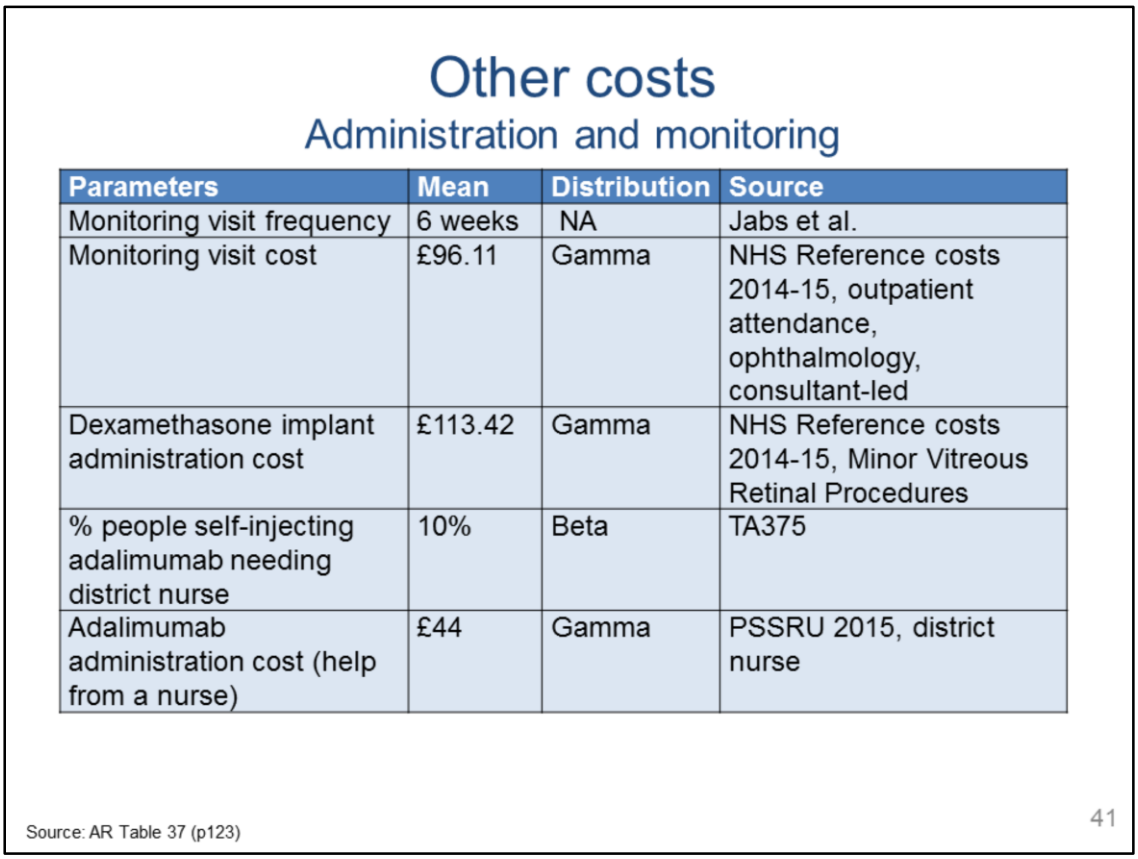
See section 6.2.1.3 (estimation of model parameters from page 119 and table 35 on page 120) in the Assessment Report for more details



Other costs

Administration and monitoring

Parameters	Mean	Distribution	Source
Monitoring visit frequency	6 weeks	NA	Jabs et al.
Monitoring visit cost	£96.11	Gamma	NHS Reference costs 2014-15, outpatient attendance, ophthalmology, consultant-led
Dexamethasone implant administration cost	£113.42	Gamma	NHS Reference costs 2014-15, Minor Vitreous Retinal Procedures
% people self-injecting adalimumab needing district nurse	10%	Beta	TA375
Adalimumab administration cost (help from a nurse)	£44	Gamma	PSSRU 2015, district nurse

Source: AR Table 37 (p123)

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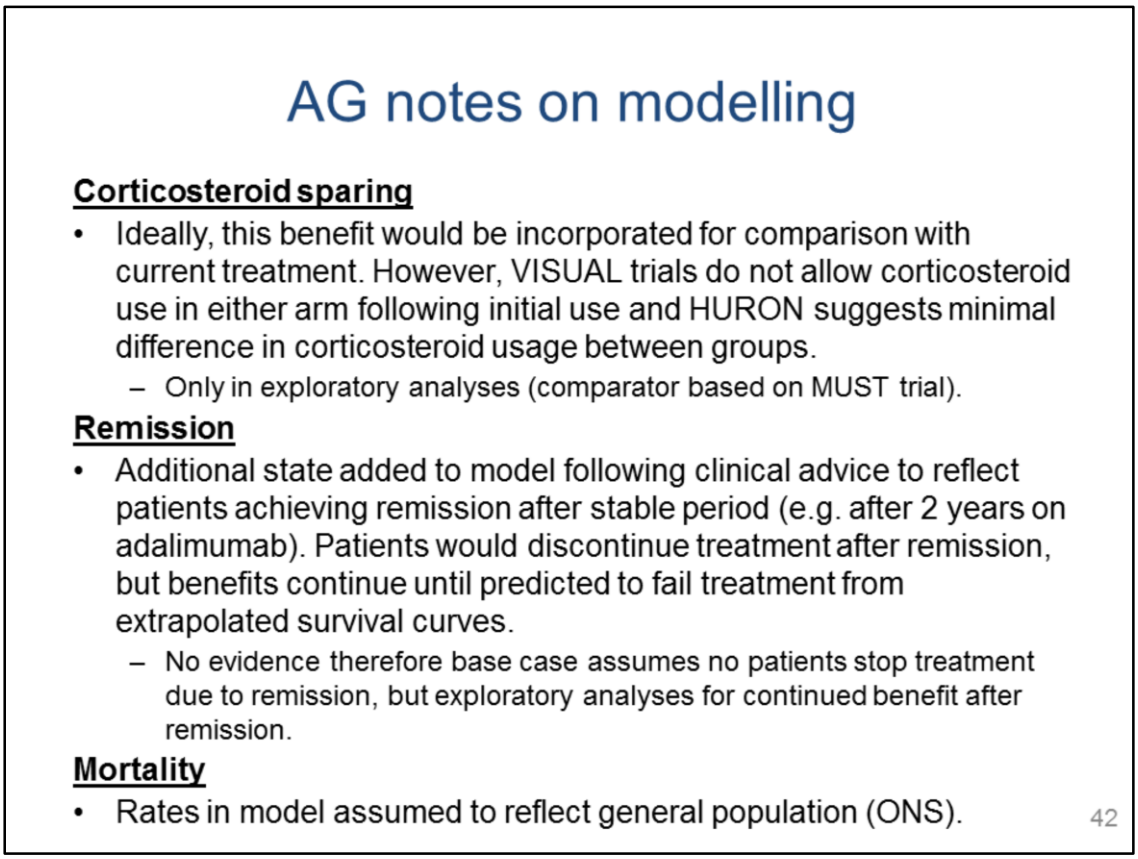
See section 6.2.1.3 (estimation of model parameters on page 119) in the Assessment Report for more details

Adalimumab is assumed to be self-administered; the base case model assumes that 10% of patients will need help from a district nurse to administer the injections, at a cost of £44 based on PSSRU 2015 (district nurse cost per hour). All other treatments would be administered by the patient and therefore there would be no extra costs of administration for corticosteroids or immunosuppressants. The model assumes that all patients would receive monitoring every 6 weeks, irrespective of treatment. Monitoring consists of outpatient visits for visual function monitoring to assess the efficacy of the treatments and to monitor the risk of AEs. The AG assumed that monitoring for AEs was conducted alongside regular visual function monitoring follow-ups. It also assumed that patients receiving immunosuppressants would receive 6 additional blood monitoring visits annually.



See section 6.2.1.3 (estimation of model parameters on page 121) in the Assessment Report for more details

Summary of model assumptions

	Adalimumab	Dexamethasone
Population	Adults with non-infectious uveitis with active disease (VISUAL I) and inactive disease (VISUAL II)	Adults with non-infectious uveitis with active disease (HURON)
Intervention dose	Adalimumab 40mg every two weeks until treatment failure	0.7mg dexamethasone implant
Stopping treatment	Parametric survival curve of time to treatment failure fitted to VISUAL I and II trial data	Patients are only given one dexamethasone implant
QALYs (during trial period)	EQ-5D measured until treatment failure, when patients revert to baseline utility, adjusted for age.	Estimate EQ-5D data using VFQ-25.
QALYs (following trial period)	Not failed treatment: retain the averaged utility from month 12 to 18 of the trial, adjusted for age. Fail treatment: revert to baseline utility, adjusted for age.	Assumes utility remains the same for four weeks following the trial (26 weeks) and then returns to baseline by week 30, adjusted for age.

Key: QALY, quality adjusted life years.
Source: Table 29 in Assessment Report (p100)

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See table 29 on page 96 of the Assessment Report for more details

Summary of model assumptions

	Adalimumab	Dexamethasone
Adverse events (except blindness)	Cataract, raised intra ocular pressure, glaucoma, serious infections, hypertension, fractures, diabetes. Additional cost only as impact on HRQoL already modelled.	
Permanent blindness (comparator)	No blindness prior to treatment failure. Constant rate of blindness after treatment failure based on Dick at al. 2016	Constant rate of blindness based on Dick at al. 2016
Permanent blindness (intervention)	No blindness prior to treatment failure. Constant rate of blindness after treatment failure based on Dick at al. 2016	Relative risk for blindness of 0.5 for 30 weeks following implantation
Treatment after remission	Treatment continues until treatment failure	

Key: QALY, quality adjusted life years..
Source: Table 29 in Assessment Report (p100)

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See table 29 on page 96 of the Assessment Report for more details

Base-case cost effectiveness results

Base case	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER
Clinical practice	14.613	£39,655	-	-	-
Dexamethasone plus clinical practice	14.641	£40,235	0.029	£580	**£20,058**
Active uveitis					
Clinical practice	14.919	£47,186	-	-	-
Adalimumab plus clinical practice	15.110	£65,401	0.191	£18,215	**£95,506**
Inactive uveitis					
Clinical practice	15.244	£48,111	-	-	-
Adalimumab plus clinical practice	15.361	£85,462	0.116	£37,351	**£321,405**

- Probabilistic ICERs for all treatments were similar to deterministic results (£19,509 for dexamethasone, £94,523 for adalimumab active disease and £317,547 per QALY gained for adalimumab inactive disease.

Source: AR Table 39 and 40 (p129)

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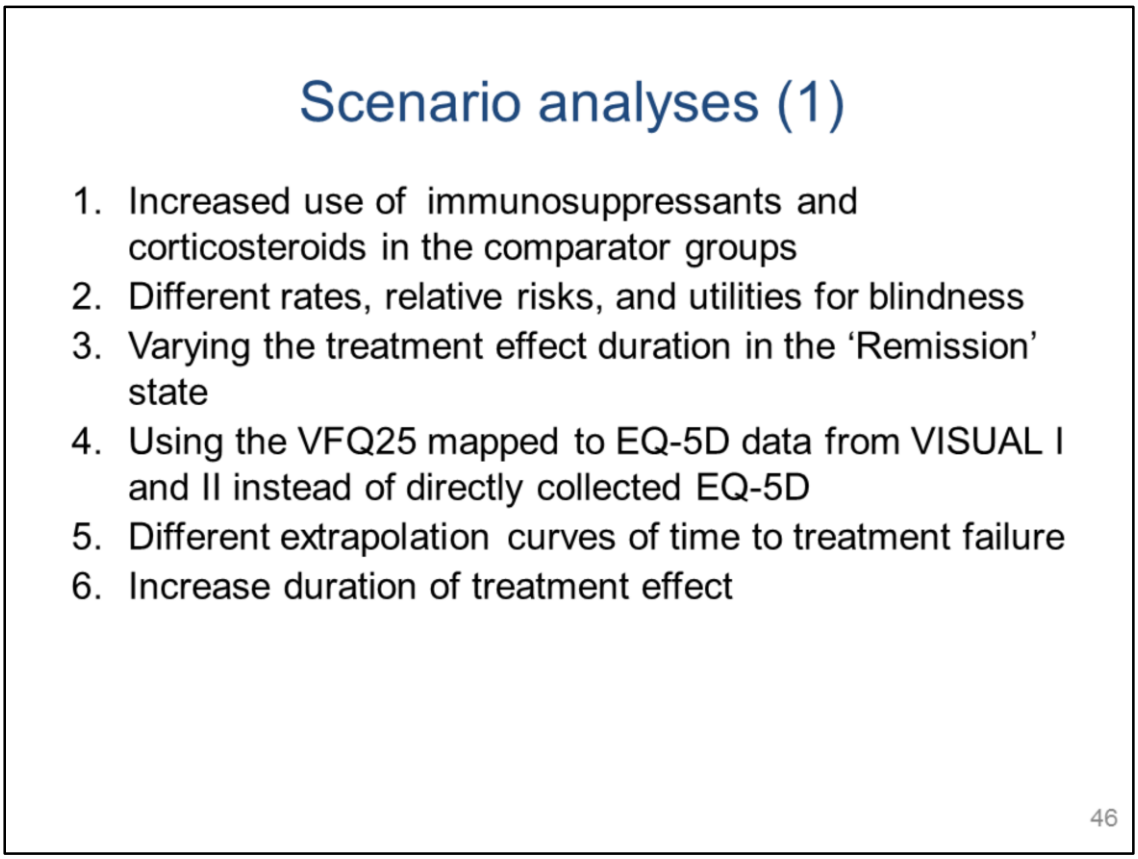
See section 6.2.2 (results from page 129) in the Assessment Report for more details

For dexamethasone the small differences in both costs and QALYs between the two groups mean that the ICER is very sensitive to alternative model parameters and assumptions, as shown within subsequent sensitivity analyses.



See section 6.2.1.4 (Model evaluation methods from page 125) in the Assessment Report for more details

1. Increased use of immunosuppressants and corticosteroids in the comparator groups-In clinical practice, it would be expected that a higher proportion of patients would receive systemic therapy. This would result in greater efficacy associated with the comparator, with a higher adverse event rate and higher costs.

2. Different rates, relative risks, and utilities for blindness-There is limited evidence around rate of legal blindness for this group, and no evidence around the impact of treatment on this rate, so the AG performed exploratory analyses around these parameters. This was done by varying the rate of legal blindness in patients with uveitis treated with (limited) current practice (from 0 to 0.0374) using alternative sources.

3. Varying the treatment effect duration in the 'Remission' state-A proportion of patients who continue treatment with adalimumab may achieve remission. The base case analysis assumes that these patients would continue to receive adalimumab until treatment failure; however, the clinical advisors to the AG suggested that after around two years of stable disease, patients may no longer require treatment but because they are in remission they may maintain the same level of HRQoL as that whilst on treatment

4. Using the VFQ25 mapped to EQ-5D data from VISUAL I and II instead of directly collected EQ-5D-This sensitivity analysis assesses the impact of using the EQ-5D data directly: (a) adjusting for the baseline differences between the placebo and adalimumab arms of the trials by using the average baseline EQ-5D from the trial, and; (b) adjusting the baseline utilities to be equivalent to those from the HURON trial to be more representative of UK utility values

5. Different extrapolation curves of time to treatment failure-The impact of using alternative plausible parametric distributions (Weibull, Gompertz) for time to treatment discontinuation was explored.

6. Increase duration of treatment effect-The treatment effect beyond six months for dexamethasone and beyond treatment discontinuation for adalimumab is unknown. Within the base case, patients receiving dexamethasone are assumed to take four weeks to return to baseline utility beyond the trial follow-up of six months. HRQoL for patients receiving adalimumab is assumed to return to baseline immediately upon treatment discontinuation. Within this exploratory analysis, for dexamethasone this time period is varied from 0 to 8 weeks, and for adalimumab this time period is increased to four weeks.

Scenario analyses (2) excluding blindness

Scenario	ICER vs limited clinical practice		
	DEX	Adalimumab (active)	Adalimumab (inactive)
AG base case	**£20,058**	**£95,506**	**£321,405**
1. Increased immunosuppressants and corticosteroids in comparator groups	£19,899*	£109,044*	Not reported
3. Add remission state for adalimumab (annual discontinuation 0.10, 0.25 or 1†)	NR	£35,299 to £95,506	£84,132 to £199,031
4. Use HRQoL VFQ25 mapped to EQ-5D	NR	£92,884	£348,094
5. Alternative parametric curves for time to treatment stopping (base case uses Log normal)	NR	£101,429 and £103,369	£297,746 and £235,916
6. Increase duration of dex treatment effect from 30 weeks to 34 weeks	£16,692	Not reported	Not reported
6. Duration of treatment effect 42 weeks	£12,154	Not reported	Not reported

Abbreviations: DEX dexamethasone; NR not reported *from probabilistic analyses, †lower ICERs associated with rate 1.00.

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See section 6.2.2 (results from page 131 for dexamethasone, page 136 for adalimumab for active disease and page 143 for adalimumab for inactive disease) in the Assessment Report for more details

Scenario analyses (3) blindness (scenario 2)

- The higher the rate of blindness, the greater the impact of the relative risk on the ICER.
- Scenario analyses also assess impact of:
  - Increasing utilities for blindness (from Czoski-Murray [2009] to Brown et al [1999]) **ICERs increase**
  - Increasing annual cost for blindness and transition to blindness- generally **ICERs decrease**

Annual blindness rate	ICER range when varying relative risk of blindness from 0 (no blindness before treatment failure) to 1 (no effect)		
	Dexamethasone	**Adalimumab (active)**	**Adalimumab (inactive)**
Base case: 0.0066 (Dick et al 2016)	£8,688 to £50,627	£95,506 to £194,471	£514,958 to £5,133,625
0.0038 (Tomkins-Netzer et al 2014)	£17,100 to £49,915	£121,908 to £193,740	£821,798 to £4,988,973
0.0374 (Durrani et al 2004)	Dominates with relative risk 0 to £56,329	£33,003 to £202,592	£141,538 to £7,411,362

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See section 6.2.2 (results from page 131 for dexamethasone [tables 42 to 44], page 136 for adalimumab for active disease [tables 50 to 52] and page 143 for adalimumab for inactive disease [tables 59 to 61]) in the Assessment Report for more details

The impact of relative risks upon the ICER for dexamethasone plus clinical practice versus clinical practice alone is very important and there is no evidence describing the impact dexamethasone will have upon the rate of blindness. For all treatments, the higher the rate of blindness, the greater the impact of the relative risk upon the model results.

Univariate sensitivity analyses

- Univariate sensitivity analyses for parameters including utility values, administration and monitoring, and adverse event costs
  - Dexamethasone: All ICERs <£21,807 per QALY gained
  - Adalimumab for active disease: All ICERs >£88,602 per QALY gained
  - Adalimumab for inactive disease: All ICERs >£300,000 per QALY gained

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See Assessment Report for more details:

- Dexamethasone: Table 46
- ADA active: Table 56
- ADA inactive: Table 65

And Table 38 for values used in univariate sensitivity analyses

Results summary
Dexamethasone

- The base case analysis estimated the ICER of one dexamethasone implant in one eye for a combination of patients with unilateral and bilateral uveitis compared with limited current practice as per the HURON trial only
- Exploratory analyses suggest that the rate of blindness in the comparator group and the relative risk of blindness for dexamethasone substantially impact upon the ICER: ranged from dominating to £56,329.

Base case ICER (deterministic)	Inc. QALYs	Inc. costs	ICER	Probability of cost-eff. at WTP threshold	
				£20,000	£30,000
Clinical practice	-	-	-	0.53	0.28
Dexamethasone and clinical practice	0.029	£573	£19,509	0.47	0.72

Key: Limited current practice, as provided in the HURON trial:25% of patients on anti-inflammatory or immunosuppressant medication.
Source: AR Table 39 and 41 (p129 and131)

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Results summary

Adalimumab for active uveitis VISUAL I

- Exploratory analyses suggest the ICER associated with adalimumab compared with (limited) current practice does not fall below £30,000
- The rate of blindness in the comparator group, the RR of blindness, and the proportion of patients who would be taken off adalimumab following remission and maintain the same quality of life are key drivers of the model results
- If all patients who remain on adalimumab at two years achieve remission and are taken off treatment whilst retaining quality of life, the ICER decreases to £35,299

Base case ICER (deterministic)	Inc. QALYs	Inc. costs	ICER	Probability of cost-eff. at WTP threshold	
				£20,000	£30,000
Clinical practice	-	-	-	1.00	1.00
Adalimumab and clinical practice	0.194	£18,321	£94,523	0.00	0.00

Key: Limited current practice, as provided in the VISUAL I trial: initial systemic steroid burst tapered by week 15 and around 30% of patients on systemic immunosuppressants.
Source: AR Table 48 and 49 (p135 and 136)

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Results summary

Adalimumab for inactive uveitis VISUAL II

- Exploratory analyses suggest the ICER associated with adalimumab compared with (limited) current practice remains above £82,000
- The rate of blindness in the comparator group, the RR of blindness, and the proportion of patients who would be taken off adalimumab following remission and maintain the same quality of life are key drivers of the model results
- If all patients who remain on adalimumab at two years achieve remission and are taken off treatment whilst retaining quality of life, the ICER decreases to £84,132

Base case ICER (deterministic)	Inc. QALYs	Inc. costs	ICER	Probability of cost-eff. at WTP threshold	
				£20,000	£30,000
Clinical practice	-	-	-	1.00	1.00
Adalimumab and clinical practice	0.118	£37,432	£317,547	0.00	0.00

Key: Limited current practice, as provided in the VISUAL II trial: on systemic steroids at baseline (10-35 mg/day) tapered by week 19 and around 47% of patients on systemic immunosuppressants.
Source: AR Table 57 (p142)

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Innovation

- Company for dexamethasone summarise innovations:
  - pharmacokinetic benefits as drug is cleared rapidly from the eye,
  - Other routes of administration require much higher daily doses of dexamethasone to achieve therapeutic levels in the posterior segment of the eye while exposing non-target areas of the body to corticosteroids
  - allows localised treatment of the eye without need for regular injections
  - reduction in systemic exposure to corticosteroids
- Company's submission for adalimumab does not refer to innovation.

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Potential equality issues

- Company for dexamethasone state that equality impact of recommendations for those patients for whom vision may be reduced or lost in one eye already may need to be assessed, as this group is at risk of becoming sight disabled.
- Company submission for adalimumab does not refer to equality issues.

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Key issues: Cost-effectiveness

- There is no nationally agreed treatment pathway
  - Is committee clear on the current treatments the interventions are likely to displace?
  - What are the most appropriate comparators for adalimumab and dexamethasone? Has the most appropriate comparator been used?
  - Are adalimumab and dexamethasone direct comparators, or used at different points in the pathway?
- The choice of annual rate of blindness in the comparator group and the relative risk of blindness for dexamethasone and adalimumab impacts the ICER considerably – which rates are most appropriate?
- The proportion of patients taken off adalimumab treatment following remission and maintaining the same quality of life has the largest impact upon the ICER for adalimumab – what is the most likely proportion?
- All base cases and scenarios showed adalimumab to be >£30,000
- Current treatment is associated with substantial treatment-related morbidity. Has the model adequately captured this?

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Authors

- **Marcela Haasova and Abitha Senthinathan**
  Technical Leads
- **Carl Prescott**
  Technical Adviser
- with input from the Lead Team (Gail Coster, Andrea Manca and Judith Wardle)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Adalimumab and dexamethasone for treating non-infectious uveitis

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of adalimumab and dexamethasone intravitreal implant within their marketing authorisations for treating non-infectious, intermediate, posterior or pan uveitis.

Background

Uveitis is an inflammation of the uveal tract of the eye, which consists of the iris, the ciliary body and the choroid. It is usually caused by an underlying autoimmune disorder or trauma to the eye. In some people the cause is unknown. Uveitis is classified according to the main location of inflammation. Anterior uveitis is inflammation of the iris. Intermediate uveitis affects the posterior part of the ciliary body and the vitreous humour. Posterior uveitis affects the back of the eye, including the retina and the choroid. Pan uveitis is inflammation of the whole of the uveal tract (front and back of the eye). Symptoms include pain and redness in the eye, blurred vision, sensitivity to light, loss of peripheral vision and headaches. One or both eyes may be affected.

Intermediate, posterior and pan uveitis are less common than anterior uveitis (they account for around 1 in 4 uveitis diagnoses[1]) but are more severe and more likely to cause vision loss. Consequences of uveitis include glaucoma (increased pressure inside the eye), cataracts (cloudiness of the lens) and cystoid macular oedema (swelling of the retina). Between 1500 and 5000 people are diagnosed with non-infectious intermediate or posterior uveitis each year in England[2,3]. There are no data on the incidence of pan uveitis in England.

Non-infectious intermediate, posterior and pan uveitis are initially treated with corticosteroids. Corticosteroids may be administered systemically (oral or parenteral), through periocular or intravitreal injections, or using intravitreal implants. Additionally, if the front of the eye is also affected, topical corticosteroids and dilating eye drops may be offered. People with severe or chronic non-infectious uveitis whose disease has not adequately responded to corticosteroid treatment, or for whom corticosteroids are not appropriate, may also be given immunosuppressive drugs such as methotrexate, ciclosporin, mycophenolate mofetil and azathioprine (either systemically or as an intravitreal injection). Immunosuppressive drugs can allow a reduction in the corticosteroid dose and associated complications. Immunosuppressive drugs may also be given when corticosteroids are contraindicated or not tolerated. If

the disease does not respond to these treatments, or if they are not tolerated, biological tumour necrosis factor (TNF)-alpha inhibitors may be used.

The technologies

Adalimumab (Humira, AbbVie) is a monoclonal antibody that inhibits the pro-inflammatory cytokine, TNF-alpha. It is administered by subcutaneous injection. Adalimumab does not currently have a marketing authorisation in the UK for treating uveitis. It has been compared with placebo in clinical trials in adults with active, non-infectious intermediate, posterior, or pan uveitis despite conventional therapy (that is, corticosteroids with or without immunosuppressives).

Dexamethasone intravitreal implant (Ozurdex, Actavis UK and Allergan) is a corticosteroid which suppresses inflammation by inhibiting the expression of pro-inflammatory mediators. It is a biodegradable implant which is administered by intravitreal injection. Dexamethasone has a marketing authorisation in the UK for treating inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

Intervention(s)	Adalimumab subcutaneous injection Dexamethasone intravitreal implant
Population(s)	People with non-infectious, intermediate, posterior or pan uveitis
Comparators	The interventions listed above compared with each other where appropriate, and with: • Periocular or intravitreal corticosteroid injections • Intravitreal corticosteroid implants • Systemic corticosteroids • Systemic immunosuppressive therapies including azathioprine, methotrexate, cyclophosphamide, ciclosporin, chlorambucil, tacrolimus, mycophenolate mofetil and TNF-alpha inhibitors • Intravitreal methotrexate • Best supportive care (when all other treatment options have been tried).

Outcomes	The outcome measures to be considered include: • visual acuity (the affected eye) • visual acuity (both eyes) • mortality • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye. The availability and cost of biosimilars should be taken into consideration.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	None
Related National Policy	**NHS England:** NHS England Clinical Commissioning Policy (July 2015) Infliximab (Remicade) and Adalimumab (Humira) as Anti-TNF Treatment Options for Adult Patients with Severe Refractory Uveitis NHS England (January 2014) Manual for prescribed specialised services 2013/14, chapter 12 (page 43): Adult specialist ophthalmology services **National Service Frameworks:**

	Older People **Department of Health:** Department of Health (November 2014) NHS Outcomes Framework 2015-2016. Domains 2, 4, 5.

References

1 NHS Choices website. Uveitis - overview [accessed November 2015]

2 North East Treatment Advisory Group (NETAG) 2012 Ozurdex® dexamethasone ocular implant for uveitis [accessed November 2015]

3 Committee for Orphan Medicinal Products 2010 Public summary of opinion on orphan designation: Dexamethasone (intravitreal implant) for the treatment of non-infectious uveitis affecting the posterior segment of the eye [accessed November 2015]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Adalimumab and dexamethasone for treating non-infectious uveitis [ID763]

Matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Companies • AbbVie (adalimumab) • Allergan (dexamethasone intravitreal implant) Patient/carer groups • Action for Blind People • Behcets Syndrome Society • Birdshot Uveitis Society • Eyecare Trust • Fight for Sight • Muslim Council of Britain • National Federation of the Blind of the UK • Olivia's Vision • OBAC • Royal National Institute of Blind People (RNIB) • SeeAbility • Sense • South Asian Health Foundation • Specialised Healthcare Alliance • Thomas Pocklington Trust Professional groups • Association of Optometrists • British and Eire Association of Vitreoretinal Surgeons British Diabetic • British Geriatrics Society • British and Irish Orthoptic Society • British Opthalmic Anaesthesia Society (BOAS) • College of Optometrists • Royal College of General Practitioners	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium • Uveitis Information Group (Scotland) • Wales Council for the Blind Comparator companies • Accord Healthcare (methotrexate, mycophenolate mofetil, tacrolimus) • Allergan (azathioprine, mycophenolate mofetil, oral prednisolone, azathioprine, mycophenolate mofetil, oral prednisolone) • Alimera Sciences (fluocinolone acetonide intravitreal implant) • Alkopharma (chlorambucil) • AMCo (methotrexate, injectable prednisolone) • Aspen Pharma Trading (azathioprine, chlorambucil, oral & injectable dexamethasone)

Consultees	**Commentators (no right to submit or appeal)**
• Royal College of Nursing • Royal College of Ophthalmologists • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • UK Clinical Pharmacy Association <u>Others</u> • Department of Health • NHS Bromley CCG • NHS England • NHS North Lincolnshire CCG • Welsh Government	• Astellas (tacrolimus) • Auden McKenzie (oral dexamethasone, oral prednisolone) • Baxter Healthcare (cyclophosphamide) • Beacon Pharmaceuticals (injectable prednisolone) • Boston Healthcare (oral prednisolone) • Cardinal Health Martindale Products (oral dexamethasone) • Bristol-Myers Squibb Pharmaceuticals (triamcinolone acetonide injectable suspension) • Celltrion Healthcare/Napp Pharmaceuticals (infliximab biosimilar) • Chemidex Pharma (oral dexamethasone) • Colorama Pharmaceuticals (ciclosporin, mycophenolate mofetil) • Cubic Pharmaceuticals (ciclosporin, mycophenolate mofetil) • DE Pharmaceuticals (azathioprine, ciclosporin, oral dexamethasone, methotrexate, mycophenolate mofetil, injectable prednisolone) • Dexcel (ciclosporin, tacrolimus) • Ennogen Pharma (azathioprine, ciclosporin) • E.R. Squibb & Sons (triamcinolone acetonide injectable suspension) • Ethigen (ciclosporin) • Hameln Pharmaceuticals (injectable dexamethasone, methotrexate) • Hospira UK (infliximab biosimilar, injectable dexamethasone, methotrexate) • Icarus Pharmaceuticals (ciclosporin, mycophenolate mofetil) • Medac (methotrexate) • Merck Sharp & Dohme (infliximab, oral dexamethasone) • Mylan UK (ciclosporin, mycophenolate mofetil, tacrolimus) • Niche Pharma (ciclosporin, mycophenolate mofetil)

Consultees	**Commentators (no right to submit or appeal)**
	• Novartis (ciclosporin, mycophenolate mofetil) • Orion Pharma (methotrexate) • Pfizer (cyclophosphamide, methotrexate, injectable prednisolone) • Roche (mycophenolate mofetil) • Rosemont Pharmaceuticals Ltd (oral dexamethasone) • Sandoz (methotrexate, mycophenolate mofetil, tacrolimus) • Teva UK (azathioprine, ciclosporin, cyclophosphamide, methotrexate, mycophenolate mofetil, oral prednisolone, tacrolimus) • Wockhardt (methotrexate, mycophenolate mofetil, oral prednisolone) • Zentiva UK (mycophenolate mofetil, oral prednisolone) <u>Relevant research groups</u> • British Council for Prevention of Blindness • Cochrane Eyes and Vision Group • Eye Hope • Institute of Ophthalmology, University College London • International Uveitis Study Group • MRC Clinical Trials Unit • National Eye Research Centre • National Institute for Health Research <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do share it. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees
Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators
Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that manufacture comparator technologies; NHS Quality Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1] Non-company consultees are invited to submit statements relevant to the group they are representing.

Confidential until published

Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence

Title: Adalimumab and dexamethasone for treating non-infectious intermediate, posterior or pan uveitis in adults

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Hazel Squires, Senior Research Fellow, ScHARR Edith Poku, Research Fellow, ScHARR Inigo Bermejo, Research Associate, ScHARR Katy Cooper, Senior Research Fellow, ScHARR John Stevens, Reader in Decision Science, ScHARR Jean Hamilton, Research Associate, ScHARR Ruth Wong, Information Specialist, ScHARR Alastair Denniston, Consultant Ophthalmologist (Uveitis and Medical Retina), University Hospitals Birmingham NHS Foundation Trust, UK Ian Pearce, Director of Clinical Eye Research Centre, St Paul's Eye Unit, Royal Liverpool University Hospital, UK Fahd Quhill, University Senior Lecturer and Consultant Ophthalmologist (Specialist interest in Medical Retina), Sheffield Teaching Hospitals NHS Foundation Trust, UK
Correspondence Author	Hazel Squires, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, S1 4DA UK. Email: h.squires@sheffield.ac.uk
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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Contributions of authors

Hazel Squires was the Assessment Group lead and advised on the cost-effectiveness modelling. Edith Poku and Katy Cooper undertook the clinical effectiveness review. Inigo Bermejo undertook the cost-effectiveness review and developed the cost-effectiveness model. John Stevens and Jean Hamilton commented on statistical issues and feasibility of network meta-analysis and Ruth Wong performed the literature searches. Alastair Denniston, Ian Pearce and Fahd Quhill provided clinical advice throughout the project. All authors were involved in drafting and commenting on the final report.

About ScHARR

The School of Health and Related Research (ScHARR) is one of the nine departments that comprise the Faculty of Medicine, Dentistry and Health at the University of Sheffield. ScHARR specialises in health services and public health research, and the application of health economics and decision science to the development of health services and the improvement of public health.

The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the clinical effectiveness and cost-effectiveness of healthcare interventions for the NIHR Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute for Health and Care Excellence (NICE). ScHARR-TAG is part of a wider collaboration of a number of units from other regions including Health Economics Research Unit and Health Services Research Unit, University of Aberdeen; Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Liverpool Reviews & Implementation Group (LRiG), University of Liverpool; Peninsular Technology Assessment Group (PenTAG), University of Exeter; the NHS Centre for Reviews and Dissemination, University of York; Warwick Evidence, University of Warwick; the BMJ Technology Assessment Group (BMJ-TAG), BMJ Evidence Centre and Kleijnen Systematic Reviews Ltd.

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1 DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

DEFINITION OF TERMS

Anterior chamber of the eye	The fluid-filled space of the front part of the eye located between the iris and the inner surface of the cornea.
Anterior segment of the eye	The part of the eye composed of the cornea, iris, lens, ciliary body and front part of the sclera (white part of the eye). In general, it forms the anterior (front) third of the eye.
Cataract	A cloudiness of the lens of the eye
Corticosteroid-sparing therapy	A single treatment or treatment regimen that allows the reduction or discontinuation of on-going corticosteroids
Cycloplegic drug	A drug that causes relaxation of the ciliary muscle of the eye.
Extended dominance	Where the incremental cost-effectiveness ratio for a given treatment alternative is higher than that of the next more effective (non-dominated) comparator.
Fluorescein angiography	An eye test using specialized camera and fluorescent dye to examine the circulation of the retina and choroid.
Glaucoma	An eye condition characterized by damage to the optic nerve caused by intraocular pressure.
Immunosuppression	Reducing or lowering immune response by using drugs
Indirect ophthalmoscope	A magnifying instrument with a light source for examining the inside of the eye through the pupil, especially the space between the lens and the retina.
Intraocular pressure	Pressure exerted by fluid in the eye. The normal range is between 10 to 20 mmHg and may vary in an individual at different times of the day.
Meta-analysis	A statistical method by which the results of a number of studies are pooled to give a combined summary statistic.
Macula	The pigmented area or ‘yellow spot’ near the centre of the retina
Macular oedema	Fluid collection in the region of the macula
Mydriatic drug	A drug instilled in the eye to dilate the pupil.
Posterior segment of the eye	The part of the eye encompassing the vitreous, choroid, retina and optic nerve. It forms the posterior (back) two-thirds of the eye

Optical coherence tomography	A non-invasive technique for cross-sectional imaging of the retina and light-sensitive areas of the eye.
Optic nerve	A nerve that transmits visual information from the retina to the brain.
Relative risk	Ratio of the probability of an event occurring in an exposed group relative to a non-exposed or control group
Simple dominance	Where an intervention is less effective and more expensive than its comparator.
Visual acuity	This refers to how well a person sees, i.e. clarity of vision.
Vitreous	A clear jelly-like fluid that fills the middle of the eye, between the lens and retina.

LIST OF ABBREVIATIONS

AC	Anterior chamber
ADA	Adalimumab
AE	Adverse event
AIC	Akaike Information Criterion
AG	Assessment Group
BCVA	Best corrected visual acuity
BD	Behçet's disease
BIC	Bayesian Information Criterion
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CrI	Credible interval
CRD	Centre for Reviews and Dissemination
CMO	Cystoid macular oedema
CSR	Clinical Study Report
DEX 350	Dexamethasone 0.35 mg
DEX 700	Dexamethasone 0.7 mg
EMA	European Medicines Agency
EQ-5D	EuroQol five dimensions questionnaire
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
HADS	Hospital Anxiety and Depression Scale
HLA	Haplotype association
HR	Hazard ratio
HRU	Healthcare Resource Use
HRQoL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
IOP	Intraocular pressure
ITT	Intention to treat
LCP(H)	Limited current practice based on HURON
LCP(VI)	Limited current practice based on VISUAL I
LCP(VII)	Limited current practice based on VISUAL II
LOCF	Last observation carried forward
LogMAR	Logarithm of the minimum angle of resolution,
LYG	Life years gained
NEI	National Eye Institute

NICE	National Institute for Health and Clinical Excellence
NMA	Network meta-analysis
NR	Not reported
NSAID	Non-steroidal anti-inflammatory drug
OCT	Optical coherence tomography
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRN	*pro re nata* (as needed)
PSIU	Posterior segment-involving uveitis
QALY	Quality-adjusted life years
RCT	Randomised controlled trial
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-36	36-item short form
SmPC	Summary of Product Characteristics
SUN	Standardization of Uveitis Nomenclature
TNF	Tumour necrosis factor
USA	United States of America
UK	United Kingdom
VA	Visual acuity
VFQ-25	Visual Function Questionnaire-25
VH	Vitreous haze
VKH	Vogt-Koyanagi-Harada syndrome
WHO	World Health Organisation
WPAI	Work Productivity and Activity Impairment

2 EXECUTIVE SUMMARY

2.1 Background

Uveitis describes a group of conditions characterised by inflammation inside the eye, including those structures collectively known as the uveal tract. The underlying cause of uveitis may be broadly divided into infectious and non-infectious causes. In the UK and most of the developed world the cause is most commonly non-infectious, and appears to be autoimmune in origin, either isolated to the eye or associated with a systemic autoimmune disorder. The effects of uveitis vary according to which part of the eye is affected. This assessment covers the most sight-threatening forms of non-infectious uveitis, namely those that affect the posterior structures of the eye, termed intermediate uveitis (vitreous humour and posterior ciliary body), posterior uveitis (retina and choroid) and panuveitis (front and back of the eye); it does not cover anterior uveitis (iris and anterior ciliary body). Symptoms include blurred vision, floaters in the eye, and sometimes pain and redness. Consequences of uveitis which may lead to loss of vision include early complications such as cystoid macular oedema (swelling of the retina) and vitreous haze (VH, inflammatory cell debris in the vitreous), and late complications such as cataracts (cloudiness of the lens), glaucoma (optic nerve damage associated with increased pressure inside the eye), and irreversible damage to the retina. Between 3 and 16 out of 100,000 people are estimated to have non-infectious posterior segment-involving uveitis (see Section 7). Uveitis generally presents in people of working age; it is the fifth leading cause of visual impairment in developed countries and accounts for 10% of cases of legal blindness.

In the context of this report, corticosteroids (systemic or local injection or implant) are considered first-line treatment. Immunosuppressive drugs (such as methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus and azathioprine) are considered second-line agents for uveitis unresponsive to corticosteroids or which recurs on steroid tapering. Tumour necrosis factor (TNF)-alpha inhibitors are considered as a third line treatment option. The technologies assessed here are adalimumab (Humira), a monoclonal antibody TNF-alpha inhibitor, and dexamethasone (corticosteroid) intravitreal implant (Ozurdex).

2.2 Aims

The aims of this assessment report are:

- To evaluate the clinical effectiveness and safety of adalimumab (via subcutaneous injections) and dexamethasone intravitreal implant within their marketing authorisations for treating non-infectious intermediate, posterior or pan uveitis in adults.
- To estimate the incremental cost-effectiveness of adalimumab (via subcutaneous injections) and dexamethasone intravitreal implant within their marketing authorisations

for treating non-infectious intermediate, posterior or pan uveitis, compared with each other and current treatment.

- To estimate the expected overall cost of adalimumab and dexamethasone treatment in England.
- To identify key areas for primary research.

2.3 Methods

Systematic searches undertaken in nine electronic databases up to June 2016 identified randomised controlled trials (RCTs) of adalimumab, dexamethasone implant, and relevant comparators for non-infectious intermediate, posterior or panuveitis in adults. The quality of included studies was assessed using the Cochrane Risk of Bias tool. Results were analysed via tabulation and narrative synthesis. The use of a network meta-analysis (NMA) was explored in order to compare the effectiveness of treatments.

Searches were undertaken to identify existing cost-effectiveness studies for treatments for non-infectious uveitis patients. A *de novo* Markov model was developed by the assessment group (AG) to assess the cost-effectiveness of dexamethasone compared with current practice and of adalimumab compared with current practice from an NHS and PSS perspective over a lifetime horizon. The two interventions were not compared directly as they are often used in different patient scenarios and with varying indications, and where a comparison would be clinically appropriate, there was insufficient trial evidence to support such a comparison. The cost-effectiveness of adalimumab was assessed separately for patients with active and inactive uveitis, whilst dexamethasone was assessed only for patients with active uveitis. The model includes five health states: (i) treatment: no permanent blindness; (ii) treatment failure: no permanent blindness; (iii) permanent blindness; (iv) remission; and (v) death. Effectiveness was modelled based upon Euroqol five dimensions questionnaire (EQ-5D) utility data from the VISUAL trials for the adalimumab comparison, and based on a regression analysis mapping scores from the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) reported within the HURON trial to EQ-5D utilities. Health-related quality of life (HRQoL) (defined by VFQ-25 or EQ-5D) could be improved due to a reduction in inflammation/ improvements in vision or due to a reduction in adverse events. Treatment may also reduce the risk of experiencing permanent damage to the eye, resulting in a decreased risk of permanent legal blindness. Given the uncertainties around the comparator and long term outcomes, substantial exploratory and sensitivity analyses were undertaken. An analysis was undertaken setting the rate of legal blindness to zero, which could be used to explore the cost-effectiveness of dexamethasone use in one eye in patients with unilateral disease as a separate subgroup. The

trial did not provide data separately for patients with unilateral and bilateral disease and hence it is considered to be exploratory. Owing to the lack of evidence, it was not possible to explore additional subgroups.

2.4 Results

Two RCTs of adalimumab (ADA, 40mg every 2 weeks via subcutaneous injections) versus placebo were included: VISUAL I (active uveitis, n=223) and VISUAL II (inactive uveitis, n=229). Since adalimumab is a systemic treatment, by definition both eyes were treated in all patients. All patients were on high-dose corticosteroids at baseline, over 90% had bilateral uveitis, and uveitis duration was 40-63 months. Patients in VISUAL I received an initial high-dose steroid burst; steroids were then tapered in both studies. Follow-up was up to 80 weeks or until treatment failure, and outcomes were measured from the best response following steroid burst (VISUAL I) or from baseline (VISUAL II) to treatment failure or study end.

One RCT of a single dexamethasone implant (HURON, n=229) was included, comparing doses 0.7mg (DEX 700) or 0.35mg (DEX 350) versus sham over 26 weeks. Given the licensed indication, this assessment was limited to patients in the DEX 700 and sham groups. One eye was treated per patient (right eye if bilateral; the worse-seeing eye was treated in 84% of all patients). Patients received a single implant only (no repeat implants). Within the relevant study arms of HURON, 25% of patients were receiving systemic therapies at baseline, the proportion of bilateral cases was not recorded, and uveitis duration was 51 to 61 months. Rescue therapies (local steroids or new or increased systemic treatments) were received by 38% in the treatment group and 22% in the sham group.

Thirteen additional studies of clinically-relevant comparator treatments (versus placebo or one another as per NICE scope) were identified. However, pairwise meta-analysis and network meta-analysis (NMA) were not feasible due to clinical heterogeneity, the lack of common comparators (the network was disconnected) and differences in reported outcomes between the studies. Therefore, the following sections consider only the three studies of adalimumab and dexamethasone.

Clinical effectiveness

The primary outcome for the VISUAL studies of ADA was a composite for treatment failure based on worsening of any of the following in either eye: anterior chamber (AC) cell grade; VH grade; best-corrected visual acuity (BCVA), or new inflammatory lesions. In VISUAL I (active uveitis), median time to treatment failure was 5.6 months (ADA) versus 3.0 months (placebo); hazard ratio (HR) 0.50 (95% CI 0.36 to 0.70, $p<0.001$). In VISUAL II (inactive

uveitis), median time to treatment failure was not estimable for ADA versus 8.3 months for placebo; HR 0.57 (95% CI 0.39 to 0.84, p=0.004). In VISUAL I, there were significant benefits for ADA versus placebo for changes in the following (averaged across both eyes): visual acuity (p=0.003), inflammation (VH, p<0.001 and AC cell grade, p=0.011), macular oedema (change in central retinal thickness, p=0.020), VFQ-25 composite score (p=0.010) and EQ-5D (p=0.044). In VISUAL II, differences were not significant for ADA versus placebo for changes in any of the following (averaged across both eyes): visual acuity (p=0.096), inflammation (VH, p<0.070 and AC cell grade, p=0.218), macular oedema (change in central retinal thickness, p=0.451), VFQ-25 composite score (p=0.160) or EQ-5D (p=0.836). Secondary outcomes in VISUAL I and II were only measured up to treatment failure or study end, and since treatment failure occurred in more patients in the placebo than ADA arms, results may have been worse in the placebo arms at the point of outcome measurement. The last observation carried forward (LOCF) method used for dealing with missing data may have introduced systematic bias, as it assumes that data is missing at random, which is not the case here.

In the HURON study, there were significant benefits for DEX 700 versus sham for the following (measured in the study eye only): percentage of patients with VH score of zero at 8 weeks (p<0.001) and 26 weeks (p=0.014); percentage of patients with VH improvement ≥2 units at 8 weeks (p<0.001) and 26 weeks (p=0.001); percentage of patients with BCVA improvement of ≥3 lines over weeks 3 to 26 (p<0.001); mean BCVA improvement over weeks 3 to 26 (p≤0.002); central retinal thickness at 8 weeks (p≤0.004) though not at 26 weeks (p≥0.227); change in VFQ-25 composite score (per patient as opposed to study eye) at 8 weeks (p=0.007) and 26 weeks (p=0.001), and; percentage of patients with ≥5-point improvement in VFQ-25 score at 8 weeks (p<0.001) and 26 weeks (p<0.05). Rescue medications (corticosteroid injections in the study eye or new/increased systemic corticosteroids or immunosuppressants) were required in 22% in the DEX 700 arm versus 38% for sham (p=0.030).

Since ADA affects the immune system, potential risks include infections and malignancy.[3] Serious infections were higher for ADA than placebo in VISUAL I[4] (4.5% versus 1.8%) but not VISUAL II[5] (1.7% versus 1.8%). Malignancies and chronic renal failure each occurred in a total of 3 patients across both trials (ADA) versus none (placebo). Systemic AEs which were higher for adalimumab than placebo in at least one of the VISUAL studies[4, 5] included infections, injection site reactions, fatigue, arthralgia, myalgia, paraesthesia, hypertension and liver enzyme increases. Anti-adalimumab antibodies in patients on ADA occurred in 2.7% in VISUAL I[4] and 5% in VISUAL II.[5] There was little difference between ADA and placebo in rates of ocular AEs.

Risks for DEX 700 include those associated with intraocular steroids i.e. increased intraocular pressure (IOP), cataract, glaucoma, infection and bleeding.[6] In the HURON study,[7] raised IOP occurred in 25% (DEX 700) versus 7% (sham), while IOP ≥25 mmHg occurred in 7.1% (DEX 700) versus 1.4% (sham). Glaucoma rates were lower for dexamethasone (0%) than sham (2.7%); no patients required incisional surgery for glaucoma, while 2.6% (DEX 700 group) required laser iridotomies, and at any single time-point up to 23% in the DEX 700 group required IOP-lowering medication (not reported for sham). Cataracts in eyes that were phakic (had a natural lens) at baseline occurred in15% (DEX 700) versus 7% (sham), and cataract surgery in 1.6% (DEX 700) versus 3.6% (sham). Endophthalmitis (severe eye infection) and severe uveitis worsening occurred in 1 patient each (DEX 700) versus none for sham. Conjunctival haemorrhage occurred in 30% (DEX 700) versus 21% (sham). No systemic adverse effects (AEs) were substantially higher for DEX 700 than sham.

Cost-effectiveness

The base case analysis undertaken by the AG estimated the ICER of one dexamethasone implant in one eye for a combination of patients with unilateral and bilateral uveitis compared with limited current practice as per the HURON trial, to be £19,509 per QALY gained. The ICER of adalimumab (systemic, therefore treatment for both eyes) for patients with mainly bilateral uveitis compared with limited current practice as per the VISUAL trials, is estimated to be £94,523 and £317,547 per QALY gained in patients with active and inactive uveitis respectively.

Exploratory analyses suggest that two of the factors with the largest impact upon the ICERs, both of which are highly uncertain, are the rate of blindness in the comparator group and the relative risk of blindness for adalimumab and dexamethasone. The incremental cost-effectiveness for dexamethasone compared with (limited) current practice varies from dominating to an ICER of £56,329 per QALY gained under different assumptions for these parameters. Where the rate of legal blindness is set to zero, this is used to explore the potential cost-effectiveness of dexamethasone for patients with unilateral uveitis, which has an estimated ICER of £50,627. Under all assumptions tested for these parameters, the ICER associated with adalimumab compared with (limited) current practice remains above £30,000 and £82,000 for patients with active and inactive uveitis respectively. The proportion of patients taken off adalimumab treatment following remission and maintaining the same quality of life has the largest impact upon the ICER for adalimumab, reducing it to £35,299 and £84,132 per QALY for patients with active and inactive uveitis respectively when assuming all patients go on remission after two years on adalimumab.

2.5 Discussion

There are two RCTs of ADA versus placebo (VISUAL I and VISUAL II) and one of DEX 700 versus sham (HURON). There was no evidence comparing ADA or DEX 700 against one another or against current standard care. There was a lack of data on long-term impacts of treatment or in patients with severe uveitis or those unresponsive to immunosuppressants.

The results of the health economic model are highly uncertain due to the limited availability of evidence. In addition to the issues explored within sensitivity analyses, there are a number of additional considerations resulting from the differences between the evidence and practice which was not possible to quantify. Firstly, the clinical experts to the AG suggested that the proportion of patients who remain on adalimumab treatment is likely to be underestimated within the VISUAL trials because of the strict criteria used for treatment failure. If more people were to remain on treatment, the additional group of patients on treatment would incur the same costs as those who remain on treatment in the VISUAL trial, whilst the effectiveness of adalimumab is likely to be reduced in these patients who were considered to have failed treatment in the trial, hence, the ICER would increase for these patients. Secondly, the clinical advisors to the AG suggest that for the 'inactive' group of patients, adalimumab is more likely to be used in patients who have to discontinue existing immunosuppressants because they are ineffective or not tolerated; however, there is no clinical data for this group of patients. Thirdly, the model assumes that only one dexamethasone implant would be provided to patients. There is no RCT evidence to assess the comparative effectiveness or safety of more than one dexamethasone implant, either in both eyes or consecutively. Whilst the AG have attempted to explore the impact of consecutive implants, it was not possible given the available data to consider the cost-effectiveness of providing dexamethasone implant within both eyes. However, because the costs would essentially be doubled (with the exception of some monitoring costs) and the increment in HRQoL is likely to be lower for the second eye, it is expected to be less cost-effective than treatment in one eye for a patient with bilateral disease. Fourthly, the clinicians to the AG suggest that adalimumab and dexamethasone are likely to be provided alongside other treatment options in practice. In the clinical trials, around a third of patients did receive other treatments in both arms. However, it is unclear whether the relative effectiveness of adalimumab and dexamethasone predicted within the trials would remain if alternative treatment in both the intervention and comparator groups were increased. If the relative effectiveness and costs remained the same, then the ICER would not change from the base case predicted ICER. Finally, due to the lack of evidence for a comparator which represents current practice, it is unclear how both adalimumab and dexamethasone may impact upon the use of other treatments. The model incorporates the impact of dexamethasone upon

rescue therapy, but this is based upon the analysis using a sham comparator. If dexamethasone or adalimumab led to a reduction in the use of immunosuppressants and/or corticosteroids without this impacting upon efficacy in these treatment groups, then they would be more cost-effective than currently predicted.

The population considered in the model is heterogeneous, and it may be that the interventions are more cost-effective in some groups than others. However, there is no evidence from the trials to undertake subgroup analyses. Patients have the potential to benefit more from treatment with adalimumab or dexamethasone if they have more severe uveitis, and hence the treatments are likely to be more cost-effective as the baseline disease worsens. In addition, patients with macular oedema would be more likely to go blind and hence the interventions of interest, in particular adalimumab due to the longer duration of treatment, are more likely to prevent cases of blindness and hence are likely to be more cost-effective in this group. The exploratory analysis setting the rate of blindness to zero, which could be used to explore the potential cost-effectiveness of dexamethasone for patients with unilateral uveitis, suggests that the ICER for dexamethasone compared with (limited) current practice increases substantially; however the treatment effect for the subgroup is assumed to remain unchanged since there is no evidence around this.

The analysis presented here takes an NHS and PSS perspective. However, non-infectious uveitis affects a working-age population and can reduce workplace productivity. In addition, the disease can affect leisure time. Therefore, there are likely to be additional non NHS and PSS costs and benefits of the interventions not captured within our analyses.

2.6 Conclusions

Two RCTs of systemic adalimumab and one RCT of unilateral, single dexamethasone implant showed significant benefits over placebo or sham on outcomes including visual acuity, inflammation (VH and AC cells), macular oedema (central retinal thickness), VFQ-25, and time to treatment failure. One dexamethasone implant in a mixed group of unilateral and bilateral patients has an estimated ICER of £19,509 per QALY gained compared with (limited) current practice. The ICER associated with adalimumab compared with (limited) current practice, does not fall below £30,000 per QALY gained for any analyses tested.

There is substantial uncertainty around the evidence, in particular the comparative effectiveness and cost-effectiveness of dexamethasone and adalimumab with each other and with systemic immunosuppressants and corticosteroids as would be used in practice, and how short-term improvements in visual acuity and inflammation relate to long-term effects on vision loss and

blindness. In addition, the way in which adalimumab and dexamethasone would be used in practice and the impact of the expected differences between clinical practice and the trial evidence upon estimated outcomes is uncertain. Finally, there are important subgroups for which the interventions may be more or less effective and cost-effective; however there is insufficient evidence to make robust conclusions around these.

3 BACKGROUND

3.1 Description of health problem

Uveitis is a heterogeneous group of ocular disorders involving inflammation of the uveal tract of the eye, which consists of the iris, the ciliary body and the choroid[8-10] or surrounding tissues (e.g. sclera, retina and optic nerve).[11]

Criteria for the classification of uveitis according to anatomic site of inflammation were formally developed by the International Uveitis Study Group (IUSG) in 1987.[12] This was later revised in 2004 following the Standardization of Uveitis Nomenclature (SUN) Workshop.[13] The SUN criteria included onset, duration and course of uveitis in the classification of the condition. There is currently no agreed recommendation for describing uveitis-related systemic conditions.[14] A summary of uveitis classification according to the SUN criteria[13] is presented in Table 1.

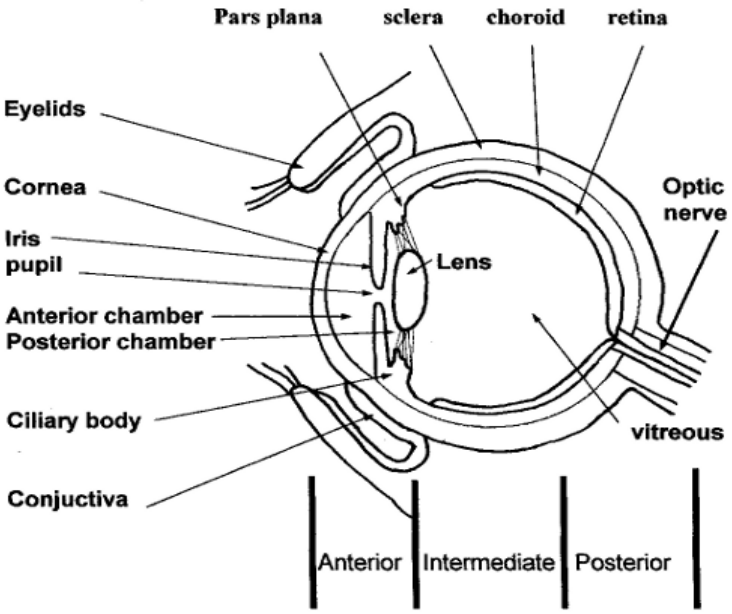
Table 1: Classification of uveitis: Standardization of Uveitis Nomenclature[13]

Type of uveitis	**Primary site of inflammation**
Anterior uveitis	Anterior chamber
Intermediate uveitis	Vitreous
Posterior uveitis	Retina and choroid
Panuveitis	Anterior chamber, vitreous, retina or choroid
Onset	**Description**
Sudden	(no detail provided)
Insidious	(no detail provided)
Duration	**Description**
Limited	Less than 3 months duration
Persistent	More than 3 months duration
Course	**Description**
Acute	Episode characterised by sudden onset and limited duration
Recurrent	Repeated episodes with intermittent periods of inactivity not requiring treatment for more than 3 months
Chronic	Persistent episode with relapse in less than 3 months treatment discontinuation

Anterior uveitis is inflammation of the anterior chamber (AC) involving the iris and the anterior aspect of the ciliary body; this is outside of the scope of this assessment. Intermediate uveitis affects the posterior part of the ciliary body and the vitreous humour. Posterior uveitis affects the back of the eye, including the retina or the choroid. Intermediate and posterior uveitis may

be referred to collectively as posterior segment-involving uveitis (PSIU). Panuveitis is inflammation of the whole of the uveal tract (front and back of the eye), extending from the AC to the choroid or retina.[8] A diagram of the eye and parts affected in anterior, intermediate and posterior uveitis is shown in Figure 1.

Figure 1: Types of uveitis based on parts of the eye affected



Source: Uveitis Information Group (Scotland) https://uveitis.net/patient/glossary.php

Intermediate, posterior and panuveitis account for around 10% of uveitis cases in the UK[15] but are more severe and more likely to cause vision loss.[16]

Aetiology, pathology and prognosis

Uveitis may be due to an infectious or non-infectious cause; this appraisal is restricted to non-infectious uveitis. Non-infectious uveitis may occur as an ocular manifestation of a systemic autoimmune condition such as Behçet's disease (BD), sarcoidosis, multiple sclerosis or Vogt-Koyanagi-Harada disease (VKH).[17, 18] A study from the Netherlands including almost 400 patients with posterior, intermediate or panuveitis reported that around half of all cases were likely to be related to systemic disease.[19] In the remaining cases, no systemic association could be found; these cases are known as idiopathic uveitis, though it is presumed that the disease is still likely to be autoimmune in nature.[18] Specific forms of uveitis include birdshot chorioretinopathy (also referred to as birdshot uveitis).

One or both eyes may be affected. Estimates of the proportion of bilateral cases from studies of uveitis patients in tertiary centres in the UK and Europe range from 41% to 67%.[16, 20-22] Each

of these centres included patients with both anterior and posterior segment-involving uveitis. Clinical advisors to the AG suggested that the proportion of bilateral cases is higher for posterior segment-involving uveitis patients only, and the proportion of bilateral cases in this group was estimated to be 70-80%. Many patients have asymmetric disease with some inflammation in both eyes but more severe disease in one eye (these patients may or may not be included in the above estimates for bilateral uveitis).

Symptoms of uveitis depend on the parts of the eye affected. The main symptoms of the forms of uveitis considered in this report include blurred vision and floaters in the eye. However, pain and redness in the eye, sensitivity to light, loss of peripheral vision and headaches may also be reported.[17] In general, clinical manifestations of uveitis of different aetiologies may be similar but treatment strategies are predominantly determined by underlying pathophysiology[23] and may often require a multidisciplinary approach.

Consequences of uveitis which may lead to loss of vision include early complications such as cystoid macular oedema (swelling of the retina) and vitreous haze (VH, inflammatory cell debris in the vitreous), and late complications such as cataracts (cloudiness of the lens), glaucoma (optic nerve damage associated with increased pressure inside the eye), and irreversible damage to the retina.[18] Many patients with posterior segment-involving uveitis require cataract surgery at a relatively early age; however, since cataract surgery is relatively efficacious and safe, clinicians may be less concerned about cataract formation than other complications of uveitis [personal communication from clinical advisors to the AG].

Dick *et al*.[24] conducted a retrospective analysis of insurance claim data from 1998 to 2012 of patients with a diagnosis of non-infectious intermediate uveitis, posterior uveitis, or panuveitis in the United States. 1769 patients with uveitis were followed up for a mean period of 5.6 years. The reported 5-year risks for patients with non-infectious intermediate uveitis, posterior uveitis, or panuveitis are as follows: glaucoma 20%, cataract 35%, visual disturbance 29%, blindness or low vision 4.5%, retinal detachment 11%, and retinal disorder 28%. The supplemental material includes a Kaplan-Meier curve of time to blindness which also reports a 10-year risk of blindness or low vision of 6.6%.

Tomkins-Netzer et al. [25] conducted a cross-sectional study of all patients (1076) who attended the uveitis clinic of a single consultant at Moorfields Eye hospital in London. The mean follow-up was 7.97 years and vision loss (BCVA $\leq$ 20/50) was reported in 19.2% of eyes. Macular scarring (4%), retinal detachment (1.33%) and chronic macular oedema (1.16%) were the most common causes of mayor vision loss, and was the most common cause for irreversible severe

vision loss (BCVA ≤ 20/200). Twenty patients had bilateral severe vision loss and were registered legally blind.

Another retrospective review of records of 315 patients with uveitis in the UK from January 1998 to December 2000 described visual impairment (BCVA ≤ 6/18 in at least one eye) in 220 of 315 (70%) uveitis patients overall, and in 149 of 192 (78%) patients with intermediate, posterior or panuveitis, after a mean follow-up duration of 36.7 months.[16] Severe visual impairment (BCVA ≤ 6/60) occurred in 38% (120/315).[16] Permanent visual impairment was present in 17% (54/315) of patients, with 15% (46/315) of patients experiencing bilateral impairment. The World Health Organisation (WHO) criteria for blindness (BVCA in better eye < 3/60 or a visual field 10°) was met in 36/315 patients (11.4%).[16] Cystoid macular oedema, cataract and the co-existence of both conditions were the predominant causes of visual loss in 26.8% (n=59/220), 17.7% (n=39/220) and 20% (n=44/220) in uveitic patients, respectively. Reported predictors of poor visual outcome were older age (*p=0.02* via logistic regression), bilateral inflammation (*p=0.0005* via t-test), panuveitis (*p=0.0005* via logistic regression) and increasing duration of reduced vision (*p=0.0005* via t-test).[16] Overall, around 10% of cases of blindness in the developed world is caused by uveitis.[22, 26]

Epidemiology and prevalence

Uveitis affects people of any age but generally presents in people of working-age, aged 20 to 50 years.[18, 23] The mean age at presentation for patients with all types of uveitis attending tertiary centres has been reported across studies in the UK,[16, 25] Netherlands[19] and France[20] as ranging from 35 years to 48 years.

There is extensive variation in causes of uveitis worldwide: genetic factors and environmental features contribute significantly to its pathology.[18] Whilst infectious uveitis is frequently seen in developing countries, idiopathic non-infectious uveitis is more common in most of the developed world, including England [23]

Earlier epidemiological studies in Europe and the US have estimated annual incidence rates of uveitis ranging from 14 to 22.5 per 100,000 people and prevalence rates of between 38 and 380 per 100,000 people.[16] Wide variations in epidemiologic statistics have been explained by differences in classification of uveitis, aetiological causes as well as demographic risk factors.[18] There are limited data on the prevalence of non-infectious posterior segment-involving uveitis in England. The Scottish Uveitis Network (SUN) reported prevalence rates for patients with uveitis treated with immunosuppression (systemic corticosteroids, second-line immunosuppressants or a combined treatment of the two agents) collected prospectively over

a 4-month period between August and November 2005; estimates ranged from 2 to 59 per 100,000 people.[27] A claims-based analysis conducted in the USA based on 2012 data from the OptumHealth Reporting and Insights claims database reported overall the prevalence of adult non-infectious uveitis (n=4,827 cases; 2,086 men and 2,741 women) to be 121 cases per 100,000 people (95% confidence interval (CI) 117.5 to 124.3).[28] Observed prevalence rates of non-infectious intermediate, posterior and pan-uveitis in adults were 1 (95% CI 0.8-1.5), 10 (95% CI 9.4-11.5), and 12 (95% CI 10.6-12.7) per 100,000 people, respectively.[28] Earlier studies generally provided no or limited data for patients with non-infectious uveitis[29, 30] or had issues (e.g. missing data, use of administrative data, variations in referral patterns) making estimates less generalisable.[27, 28, 31] Between 3 and 16 out of 100,000 people are estimated to have non-infectious posterior segment-involving uveitis (see Section 7).

Impact of health problem

Uveitis is the fifth leading cause of visual impairment in developed countries and accounts for 10% of cases of legal blindness.[28, 32] Patients may experience sudden and temporary or progressive and permanent visual impairment.[16]

By anatomic classification of uveitis, patients with posterior segment-involving uveitis and panuveitis tend to suffer more severe visual impairment than those with anterior uveitis.[32] Compared with uveitis affecting only the posterior segment, patients with panuveitis (both posterior and anterior) tend to have a poorer prognosis.[16] Additionally, the underlying cause of uveitis may also significantly influence the prognosis of intraocular inflammation.[16] For example, patients with uveitis due to Behcet's disease have poorer visual outcomes even when intense treatment is initiated at early stages of the disease compared with patients with non-infectious uveitis without an associated systemic condition.[16] Complications of uveitis, namely cystoid macular oedema, cataract, glaucoma or a combination of any of these significantly influence the visual morbidity.

Loss of visual function can lead to the inability to work and the inability to drive. It can also affect the ability to take part in leisure activities. In addition, the currently available treatments, including corticosteroids and immunosuppressants, are associated with substantial adverse events (AEs). The most common AEs associated with long-term use of corticosteroids include osteoporosis and fractures, gastric conditions, psychiatric conditions, skin conditions, hyperglycaemia, weight gain, ocular conditions (including cataract) and cerebrovascular disease.[33] The most common AEs associated with immunosuppressants include cataract, ocular hypertension, headache, fever, nausea, diarrhoea, fatigue, paraesthesia, tremors and systemic

infection.[34, 35] These can lead to substantial reductions in health-related quality of life for the patient and may also impact upon the patient's family.

Significance for the NHS

Patients with uveitis often require referral to secondary care to confirm diagnosis and provide treatment. As the cause and presentation of uveitis varies between individuals, it is important for clinicians to have a range of treatment options available. In practice, a range of unlicensed immunosuppressants and corticosteroids are used to treat patients with uveitis. Clinical advisors to the AG suggest that dexamethasone implants and adalimumab are both used variably in current practice depending on funding availability. The number of patients that would be eligible for these treatments annually is uncertain, but Allergan and Abbvie estimate that it would be 589 and 175 patients for dexamethasone and adalimumab respectively (see Section 7).

Measurement of disease

Outcome measures in uveitis may be grouped according to the different aspects that they measure: (1) disease activity or inflammation in the eye (e.g. VH, which is the degree of cloudiness in the vitreous humour; and acute cystoid macular oedema); (2) disease-associated tissue damage or complications (e.g. cataract; glaucoma; chronic cystoid macular oedema); (3) visual loss (e.g. visual acuity, visual field loss); and 4) patient-reported visual function (e.g. via the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25)).[36]

There are some issues worth highlighting about outcome measurements in patients with uveitis. Vision loss has a complex interaction with visual acuity (which is a measure of central vision according to a validated measure such as the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, Snellen chart or another similar tool), visual field contrast sensitivity and colour vision. Visual acuity in patients with uveitis may reflect both the degree of intraocular inflammation and the extent of damage in the eye; whereas inflammation may vary over short time periods (days or weeks), damage may accrue slowly (months or years) and, with the important exception of cataract and acute cystoid macular oedema, is usually irreversible. It will be immediately evident that whereas short-term effects on vision (related to inflammation) may be captured within a clinical trial, the commonly used time-frames in studies are too short to capture important long-term consequences on vision of damage to the eye caused by inadequately controlled uveitis. This may lead to systematic underestimates of the effects of such interventions in clinical trials.

Markers of structural damage to the eye, such as macular oedema (swelling of the retina), cataract and glaucoma, are important outcomes because they are the mechanisms by which uveitis patients lose vision, and are objective measures. However, these may not be good markers of whether a treatment reduces inflammation because they indicate structural damage to the eye, which might not resolve when the inflammation is treated.

In clinical practice, a combination of several outcomes is used to assess response of uveitic activity to treatment. Generally, outcomes related to uveitis are assessed by clinical examination (visual acuity, slit-lamp examination of AC cells, VH grading) and by imaging (e.g. optical coherence tomography).

The NEI system for VH grading and AC cell grading proposed by the Standardisation of Uveitis Nomenclature (SUN) Working group[13] is the '*current gold standard'* for assessing intraocular inflammation (i.e. AC cell grade and VH grade)[37] The SUN system was a formalisation and adoption of the Nussenblatt scale.[37-39] Grading requires the examination of the patient's eye by an indirect ophthalmoscope followed by a comparison of the appearance with a series of photographs of varying grades of fundus VH.[38] Although, the grading system is accepted by the Food and Drug Administration and has been used on a number of recent studies of uveitis,[37] it is a subjective grading of cloudiness in the vitreous humour caused by inflammatory cells and cell debris on a non-continuous scale (0, 0.5+, 1, 2, 3 and 4+).[12, 13, 36, 40] Its poor discriminatory property for detecting changes in the lower VH grades coupled with extensive inter-rater variations have been reported as some of its limitations.[37, 41, 42]

Inflammation in the AC is assessed on the basis of number of cells per 1 field on standard slit-lamp examination or by high-speed optical coherence tomography.[39]

Complications of structural changes in the eye due to uveitis are typically reported according to the type of complication. For example, the SUN Working Group suggests that macular oedema could be determined by clinical examination and additional tests, for example optical coherence tomography or fluorescein angiography.[13] A patient is considered to have an increased or elevated intraocular pressure (IOP) if the pressure rises above a specified limit or increases from a baseline value in a study where patients are followed over time (i.e. longitudinal data).[13] While there is no consensus reached on the threshold for considering an increase in intraocular pressure, an increase of 10 mmHg or more is considered to be important.[13] However, SUN group recommends the reporting of IOPs above the following thresholds:[13] 21 mm Hg (above the accepted upper limit of normal); 24 mm Hg (associated with a significant risk of glaucoma); and 30 mm Hg (when treatment for raised IOP is often started).

Other outcomes reported in studies of patients with uveitis include generic utility measures such as EQ-5D and vision-specific measures such as the VFQ.[43] These outcome measures capture broader considerations and hence may overcome some of the issues associated with the alternative outcome measures. The EQ-5D utility also allows treatments to be compared with treatments for other diseases and patient populations, although it may not be as sensitive as the VFQ-25.[44]

3.2 Current service provision

Non-infectious intermediate, posterior and panuveitis are initially treated with corticosteroids. Corticosteroids may be administered systemically (oral or parenteral), or locally via periocular or intravitreal injections or intravitreal implants. Additionally, if the front of the eye is also affected, topical corticosteroids and dilating eye drops may be offered. Systemic corticosteroids carry significant morbidity (e.g. cataract, glaucoma, diabetes, osteoporosis, weight gain, raised blood pressure) and long-term use above 7.5mg per day is not recommended.[45, 46]

In terms of second-line treatment, people with severe or chronic non-infectious uveitis, whose disease has not adequately responded to corticosteroid treatment, for whom corticosteroids are not appropriate, or whose uveitis recurs after tapering the corticosteroid dose, may be given immunosuppressive drugs (such as methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus and azathioprine). Immunosuppressive drugs can allow a reduction in the corticosteroid dose and associated complications. If the disease does not respond to these treatments or if they are not tolerated, especially in patients at high risk of losing their vision or those with systemic disease related to uveitis, biological TNF-alpha inhibitors may be used. The majority of these treatments are not currently licensed.

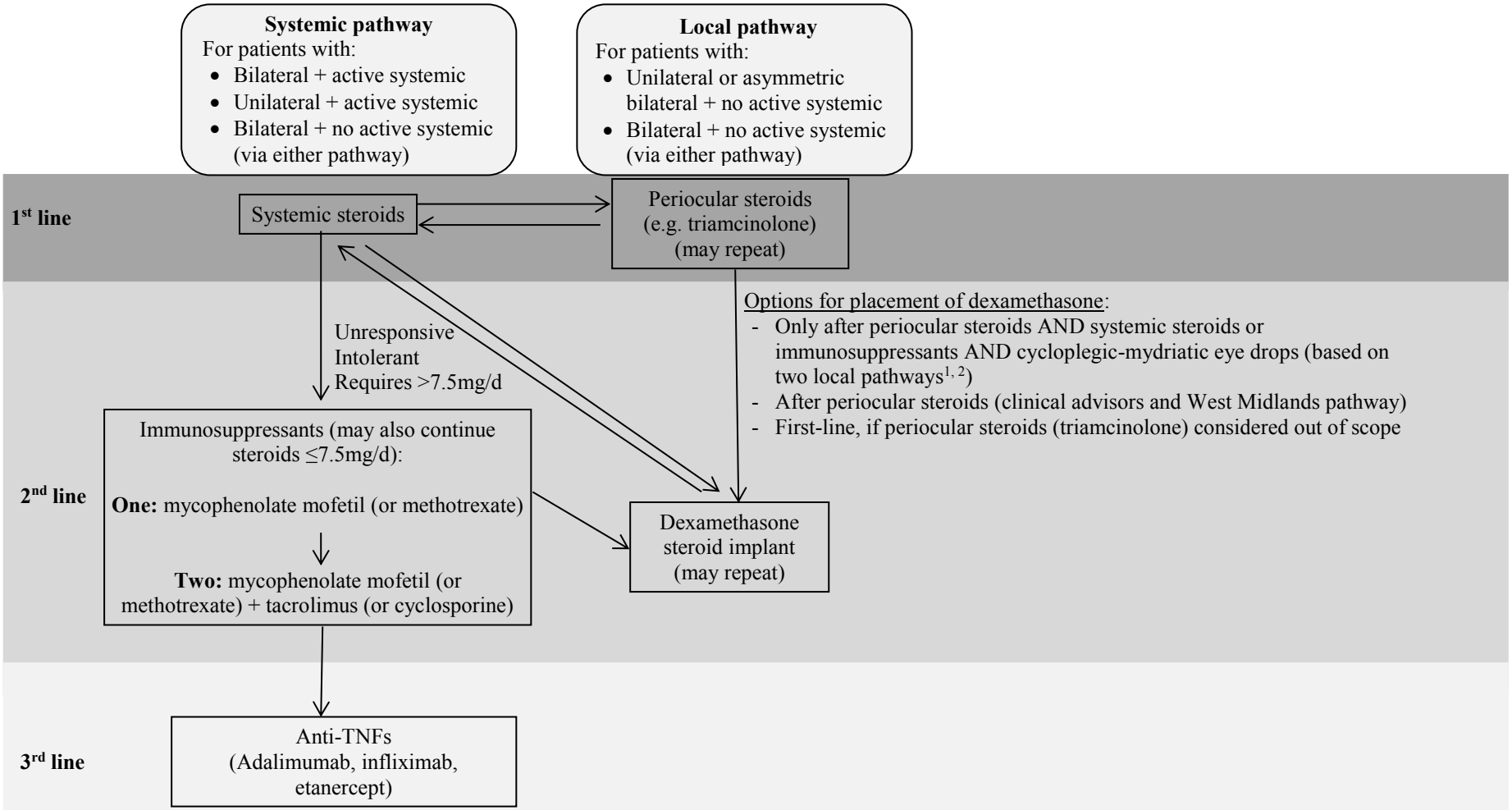
National guidelines on treating non-infectious uveitis do not currently exist; however, all three clinical advisors to the AG, who practice within different regions in the UK (Birmingham, Liverpool, Sheffield), were in agreement that the above description represents the general treatment pathway. The description is also consistent with three local treatment pathways, two referenced in the dexamethasone submission[47] (North East Retinal Group and NHS Southern Derbyshire Clinical Commissioning Group)[1, 2] and one obtained via personal communication from Alastair Denniston (August 2016) (West Midlands Regional Uveitis Service). The general treatment pathway does not differ dependent upon whether a patient has intermediate, posterior or panuveitis. However, specific treatment is individualised based upon a broad range of factors. In particular, treatment depends upon whether or not systemic disease is known to be present, whether any systemic disease is controlled (i.e. whether or not current inflammation is

restricted to the eye), and whether the disease affects one or both eyes. Figure 2 shows the general treatment pathway developed based upon three local pathways and input from the clinical advisors to the AG.

The following terminology is used in this report:

- **Systemic disease:** Known underlying systemic disease related to the uveitis
- **Active systemic disease:** Systemic disease which is currently requiring treatment (in these patients, systemic treatment may be more appropriate to treat both the uveitis and the underlying disease)
- **No active systemic disease:** Either no systemic disease related to uveitis, or systemic disease which is currently controlled (in these patients, treatment local to the eye may be more appropriate)
- **Local treatment / local pathway:** Treatments which are local to the eye (may be given to one or both eyes; little effect on systemic disease)
- **Systemic treatment / systemic pathway:** Treatments which are given systemically (and by their nature treat both eyes and may also treat systemic disease)
- **Unilateral:** Uveitis affecting one eye. This does not relate to treatment for one eye
- **Bilateral:** Uveitis affecting both eyes. This does not relate to treatment for both eyes. In the case of local treatment, it may be for one or both eyes and will be referred to as such
- **Legal blindness:** BCVA of 20/200 or less in the better-seeing eye and/or a visual field of 20 degrees or less

Figure 2: General treatment pathway in patients with non-infectious uveitis



Systemic pathway: Treatment pathway proposed for patients with severe bilateral uveitis with or without an underlying active systemic condition **or** uveitis in one or both eyes in the presence of an active systemic disease.
Local pathway: Treatment pathway proposed for patients with unilateral uveitis or asymmetrically 'severe' bilateral uveitis with no active systemic condition. Unilateral uveitis may be a first episode or a re-activation of a previous inflammation (flare).
Source: Based on three local pathways (North East Retinal Group 2012,[1] Southern Derbyshire CCG 2015[2] and West Midlands Regional Uveitis Service [personal communication]) and clinical advice.

3.3 Description of technology under assessment

Adalimumab (Humira, AbbVie) is a monoclonal antibody that inhibits the pro-inflammatory cytokine, TNF-alpha. Adalimumab has a marketing authorisation from the European Medicines Agency (EMA) for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing or in patients for whom corticosteroid treatment is inappropriate.[3] Adalimumab is administered as a subcutaneous injection containing 40 mg preparation of the active drug.

Dexamethasone intravitreal implant (Ozurdex, Allergan) is a corticosteroid which suppresses inflammation by inhibiting the expression of pro-inflammatory mediators. Dexamethasone implant has a marketing authorisation from the EMA for treating adults with inflammation of the posterior segment of the eye presenting as non-infectious uveitis (i.e. intermediate, posterior and panuveitis). Dexamethasone intravitreal implant is a biodegradable ophthalmic implant which contains 0.7mg of the active drug. Each implant is intravitreally administered using a single-use solid polymer drug delivery system or applicator.[6] The Summary of Product Characteristics (SmPC) for dexamethasone notes that administration to both eyes concurrently is not recommended due to lack of data.[6]

Place of the interventions in the treatment pathway

Clinical advisors to the AG and three local treatment pathways[1, 2] from the North East Retinal Group and the NHS Southern Derbyshire Clinical Commissioning Group[1, 2] (as referenced in the dexamethasone submission)[47] and the West Midlands Regional Uveitis Service (personal communication from clinical advisor) were consulted to determine the place of the interventions in the treatment pathway. A general view was that dexamethasone and adalimumab would generally not be used for the same patients or at the same point in the pathway. Treatments local to the eye (including the dexamethasone implant) are considered to be appropriate for unilateral uveitis or asymmetric bilateral uveitis (where disease is more severe in one eye), where systemic disease is not present or is well-controlled. Systemic treatments (including adalimumab) are considered to be appropriate to treat patients with bilateral uveitis (i.e. affecting both eyes) and/or active systemic disease. According to clinical advice to the AG, systemic treatments would generally not be given to a patient with unilateral uveitis and no active systemic disease, because of the adverse effects associated with them. Patients with bilateral uveitis but no active systemic disease could be treated via either a local or systemic approach. Whilst the inclusion criteria for the clinical trials of these drugs were not limited by these factors, our clinical experts suggest that clinicians may have selected patients for the trials accordingly.

In addition, the licensing of adalimumab and dexamethasone differ in that to be eligible for adalimumab, patients must have had an inadequate response to corticosteroids, require steroid-sparing treatment, or corticosteroid treatment must be inappropriate, whereas dexamethasone implants could be used first-

line. Clinical advisors to the AG suggest that in practice it is likely that dexamethasone would be used second-line following local or systemic corticosteroids, whilst adalimumab would be used as a third-line option for patients with insufficient control with, or intolerance to, systemic corticosteroids and immunosuppressants; however, for some patients this may be as a result of current funding availability rather than clinical need. Figure 2 shows the general treatment pathway with the most likely place of dexamethasone and adalimumab (based on the opinion of the clinical advisors to the AG).

Whilst for most patients there is a clear clinical rationale for providing dexamethasone and adalimumab at different points in the treatment pathway and for different reasons, the licensing allows both treatments to be given at overlapping points in the pathway (i.e. for patients with inadequate response to corticosteroids, in need of corticosteroid-sparing or in whom corticosteroid treatment is inappropriate),[3] although dexamethasone implant is also licensed in a less restricted group.[6] This overlap is reflected somewhat by their use in clinical trials (see Section 5). **Error! Reference source ot found.** presents the situations in which adalimumab and dexamethasone may be used according to both licensing and clinical appropriateness. The most likely places in the pathway where these treatments would be used according to clinicians are shown in bold.

Table 2: Situations in which adalimumab and dexamethasone may be used

	Unilateral (or temporary flare in one eye)*	**Bilateral**	**Unilateral (or temporary flare in one eye)**	**Bilateral**
	No active systemic disease	**No active systemic disease**	**Active systemic disease**	**Active systemic disease**
Line of therapy (see Figure 2):	Local treatment appropriate	Systemic or local treatment appropriate	Systemic treatment appropriate	Systemic treatment appropriate
First line	Dexamethasone or Adalimumab licensed if corticosteroid treatment is inappropriate			Adalimumab licensed if corticosteroid treatment is inappropriate
Second line (after systemic corticosteroids)	**Dexamethasone** or Adalimumab[◊]	**Dexamethasone** or Adalimumab[◊]	**Dexamethasone** or Adalimumab[◊]	Adalimumab
Third line (after systemic corticosteroids and immunosuppressants)	Dexamethasone or Adalimumab[◊]	Dexamethasone or **Adalimumab**	Dexamethasone or **Adalimumab**	**Adalimumab**

*Adalimumab is not clinically appropriate for unilateral non-systemic disease due to side effect profile of systemic therapies

[∝]Dexamethasone is not clinically appropriate for control of active systemic disease

[◊]In practice adalimumab would only be used if there was a specific contraindication to dexamethasone

In addition to the issues described above, because uveitis covers a heterogeneous group of diseases, clinical advice suggests that maintaining a range of options is important depending upon the patient's requirements.

Identification of important sub-groups

The following have been identified as important subgroups which might affect the treatment offered.

- Unilateral or bilateral uveitis
- Presence or absence of underlying autoimmune or inflammatory disease
- Whether any underlying systemic disease is active or controlled
- Existing treatment with long term systemic immunosuppressants
- Baseline visual acuity
- Patients for whom systemic or local corticosteroid treatments were not appropriate

Current usage in the NHS

Dexamethasone implants and subcutaneous adalimumab injections are both used variably in current practice, which may partly depend on funding availability and/or clinician and patient preference.

Anticipated costs associated with intervention

Table 3 shows the six monthly costs of dexamethasone and adalimumab. One dexamethasone implant is expected to last around 6 months based upon observational trial data and clinical advice.[22, 48, 49] It should be noted that patients could receive more than one implant, either in succession or in the other eye with staggered implementation; however these options have not been assessed within a randomised-controlled trial (RCT). Adalimumab is administered every two weeks until treatment failure and the six-monthly cost of treatment is presented in Table 3 for comparison. In the VISUAL I trial of adalimumab in active patients, 50% of patients had failed on treatment by 6 months, and 66% had failed by one year.[50] Clinical advisors to the AG suggest that some patients may remain on adalimumab treatment for many years.

Table 3: Cost of adalimumab and dexamethasone implant

Drug	Licensed dose	Company	Price	Six monthly cost (£)
Adalimumab	40 mg once every two weeks	AbbVie	£3,52.14	£4,578
Dexamethasone	One 0.70 mg implant	Allergan	£870	£870

4 DEFINITION OF THE DECISION PROBLEM

This assessment assesses the clinical effectiveness and cost-effectiveness of adalimumab (via subcutaneous injections) and dexamethasone intravitreal implant for treating inflammation of the posterior segment of the eye presenting as non-infectious uveitis. Adalimumab is licensed for the treatment of non-infectious intermediate, posterior and pan uveitis in adult patients who have had an inadequate response to corticosteroids, or are in need of corticosteroid-sparing therapy, or for whom corticosteroid treatment is inappropriate, while dexamethasone intravitreal implant is licensed for the treatment of adults with inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

4.1 Decision problem

The decision problem has been specified as follows:

Population

Adults (≥18 years) with non-infectious intermediate, posterior or panuveitis

Interventions

- Adalimumab (via subcutaneous injections) (Humira, AbbVie)
- Dexamethasone intravitreal implant (Ozurdex, Allergan)

Relevant comparators

Relevant comparators included:

- Periocular or intravitreal corticosteroid injections
- Intravitreal corticosteroid implants
- Systemic corticosteroids
- Systemic immunosuppressive therapies including azathioprine, methotrexate, cyclophosphamide, cyclosporine, chlorambucil, tacrolimus, mycophenolate mofetil and TNF-alpha inhibitors
- Intravitreal methotrexate
- Best supportive care (when all other treatment options have been tried)
- Placebo or sham

Combinations of the above treatments were also considered as relevant comparators.

Outcomes

The following outcomes were considered relevant for this assessment.

- visual acuity (the affected eye)

- visual acuity (both eyes)
    - measured as mean difference in BCVA according to a validated measure such as the ETDRS chart, Snellen chart or a similar tool
    - other measures of visual acuity will be considered if outcomes can be justified and validated in relation to accepted relevant standard measures
- improvement in disease activity (e.g. VH grade, AC cell grade)
- uveitis-related tissue damage or complication (e.g. cataract, macular oedema, retinal vascular occlusion)
- reduction in systemic steroid use
- mortality
- adverse effects of treatment
- health-related quality of life
    - including generic measures such as EQ-5D and functional measures such as the VFQ-25
- Composite endpoints incorporating more than one of the above

4.2 Overall aims and objectives of assessment

The aims of the assessment are:

1) To evaluate the clinical effectiveness and safety of adalimumab subcutaneous injection and dexamethasone intravitreal implant within their marketing authorisations for treating non-infectious intermediate, posterior or panuveitis in adults.
2) To estimate the incremental cost effectiveness of adalimumab subcutaneous injection and dexamethasone intravitreal implant within their marketing authorisations for treating non-infectious intermediate, posterior or panuveitis, compared with each other and current treatment.
3) To estimate the expected overall cost of adalimumab and dexamethasone in England.
4) To identify key areas for primary research.

5 ASSESSMENT OF CLINICAL EFFECTIVENESS

A systematic review was undertaken to assess the clinical effectiveness and safety of adalimumab subcutaneous injection and dexamethasone intravitreal implant within their marketing authorisations in adults with non-infectious intermediate, posterior or panuveitis. The review of the evidence of clinical effectiveness was carried out in accordance to the principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[51] Section 5.1 presents the methods of the systematic review of the clinical effectiveness evidence. Results of the review are reported in Section 5.2.

5.1 Methods for reviewing effectiveness

A registered protocol of this systematic review (CRD42016041799) is available on the PROSPERO website at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016041799.

5.1.1. Identification of studies

The scope of the searches took into account the potential need to make simultaneous comparisons between all interventions, including, where appropriate, a NMA. The search strategy was designed to identify RCTs and systematic reviews of the relevant interventions, adalimumab and dexamethasone intravitreal implant, as well as studies reporting on any comparators relevant to the scope, in patients with non-infectious intermediate uveitis, posterior uveitis and/or panuveitis. Given the broad range of possible comparators, the searches consisted only of terms for "uveitis" combined with search filters for relevant study types, and did not include terms for the interventions.

The search strategy comprised Medical Subject Headings (MeSH) or Emtree Thesauri terms and free-text synonyms for 'uveitis'. Searches were translated across databases and were not limited by language or publication date. The MEDLINE search strategies are presented in Appendix 1. Search filters designed to retrieve clinical trials, systematic reviews and economic evaluations were used on MEDLINE and other databases where appropriate.

a) Electronic database searches

The search approach involved the following:

- Searching of electronic databases and clinical trials registries
- Contact with experts in the field
- Examination of bibliographies of retrieved papers

The following electronic databases and clinical trials registries were searched from inception for trials and systematic reviews

- MEDLINE: Ovid, 1946 to Present
- MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations: Ovid, 1946 to Present
- EMBASE: Ovid, 1980 to present
- Cochrane Database of Systematic Reviews (CDSR): Wiley Interscience, 1996 to present
- Database of Abstracts of Reviews of Effects (DARE): Wiley Interscience, 1995 to 2015
- Cochrane Central Register of Controlled Trials (CCRCT) : Wiley Interscience, 1995 to present
- Health Technology Assessment Database (HTA) : Wiley Interscience, 1995 to present
- NHS Economic Evaluation Database (NHS EED) : Wiley Interscience, 1995 to 2015
- Cumulative Index to Nursing and Allied Health Literature (CINAHL): EBSCO, 1982 to present
- Conference Proceedings Citation Index (CPCI): Thomson Reuters, 1990 to present
- WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/) [Accessed online 15th June 2016]

Literature searching was undertaken in June 2016. Further searches were conducted in MEDLINE and CINAHL in October 2016.

b) Supplementary searches

References of relevant systematic reviews, primary studies and company submissions were checked to identify additional studies. Citation searching using Web of Science Citation Index: Thomson Reuters, 1899 to June 2016, was also undertaken. Searches were also conducted in TOXLINE to identify records reporting adverse events for the technologies of interest.

5.1.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria for selecting studies with relevant clinical effectiveness and safety data for adalimumab subcutaneous injection, dexamethasone intravitreal implant or clinically relevant comparators in adults with non-infectious intermediate, posterior or panuveitis were consistent with the decision problem outlined in the NICE scope.[52]

a) Population

The population of interest was adults with non-infectious intermediate, posterior or panuveitis. Eligible participants were considered for inclusion regardless of type of non-infectious posterior segment-involving uveitis (i.e. active or inactive uveitis; unilateral or bilateral uveitis; presence or absence of uveitis-related systemic disease or previous treatments for uveitis). Patients with infectious uveitis or

uveitis as part of a masquerade syndrome were excluded from this review. In terms of patient age, studies were eligible if the enrolled patients were aged ≥18 years, or if separate data were provided for adults, or if at least 80% of patients were adults. Studies conducted in paediatric populations were excluded.

b) Intervention

Interventions of interest were adalimumab subcutaneous injection (40mg) and dexamethasone intravitreal injection (0.7mg).

c) Comparators

Relevant comparators considered were as outlined in the NICE scope.[52] Studies reporting a comparison of adalimumab subcutaneous injection or dexamethasone intravitreal injection compared with one another or with any of the following were considered for inclusion. In addition, studies containing any of the following comparator treatments were considered for inclusion in a potential NMA:

- Periocular or intravitreal corticosteroid injections
- Intravitreal corticosteroid implants
- Systemic corticosteroids
- Systemic immunosuppressive therapies including azathioprine, methotrexate, cyclophosphamide, ciclosporin, chlorambucil, tacrolimus, mycophenolate mofetil and TNF-alpha inhibitors
- Intravitreal methotrexate
- Best supportive care (when all other treatment options have been tried)
- Placebo or sham procedure

Combinations of the above-mentioned interventions were also considered as relevant comparators.

Comparative studies in uveitis including interventions not specifically covered in the scope, or not considered to be clinically relevant comparators following consultation with clinical advisors to the AG, were excluded from the review. Excluded interventions included: sirolimus, secukinumab, bevacizumab, acetazolamide, diclofenac, lisinopril, vitamin E, retinal antigens, echinacea and vitrectomy.

d) Outcomes

Outcomes of interest were as follows:

- visual acuity (the affected eye)
- visual acuity (both eyes)

    - measured as mean difference in BCVA according to a validated measure such as the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, Snellen chart or a similar tool
    - other measures of visual acuity if outcomes were justified and validated in relation to accepted relevant standard measures
- improvement in disease activity (e.g. VH grade, AC cell grade)
- uveitis-related tissue damage or complication (e.g. cataract, macular oedema, retinal vascular occlusion)
- reduction in systemic corticosteroid use
- mortality
- adverse events
- health-related quality of life
    - including generic measures such as EQ-5D and functional measures such as the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25)
- composite endpoints incorporating more than one of the above.

e) Study design

Data from randomised controlled trials (RCTs) were considered to be the most relevant for inclusion in the systematic review of the clinical effectiveness and safety of adalimumab subcutaneous injection and dexamethasone intravitreal implant.

In addition, the dexamethasone company submission [47] included efficacy and safety data from non-randomised retrospective studies of DEX 700 for non-infectious posterior segment-involving uveitis, reported in English which included at least 10 patients. These data are summarised here for information, since some non-RCTs assessed dexamethasone repeat implants (in the same eye) or implants in both eyes, while the RCT of dexamethasone only assessed one implant in one eye per patient. It was beyond the scope of this assessment to undertake further searches or to check the study selection and data extraction undertaken within the dexamethasone company submission. Non-randomised studies of adalimumab are not included here as they were not provided in the company submission and it was beyond the scope of this assessment to undertake a *de novo* review of non-randomised studies of adalimumab.

The following publication types were excluded from our review: narrative reviews; systematic reviews; clinical guidelines; editorials; letters; opinion pieces; abstracts with insufficient detail to assess study quality or results; and non-English articles. Studies of animal models, pre-clinical and biologic studies were not included.

5.1.3 Study selection process

Study selection was undertaken using a two–stage process guided by pre-specified inclusion and exclusion criteria as presented in Sections 5.1.2.

All retrieved records were exported into a reference management database (EndNote, version X7). After de-duplication, records were assessed for relevance by initially examining titles/abstracts followed by a detailed scrutiny of the related full text versions of potentially includable studies. At each step, studies which did not satisfy the eligibility criteria were excluded. One reviewer (EP or KC) checked a set of records; this was followed by a 10% check of selected studies by a second reviewer (KC or EP). Disagreements were resolved by discussion, and involvement of a third researcher (HS) if needed.

5.1.4 Data extraction

Data were extracted by one reviewer (EP or KC) using a standardised piloted data extraction form, and checked by a second reviewer (KC or EP). Disagreements were resolved by discussion. Data relevant to the decision problem were extracted with no blinding to authors or journal. In relation to the interventions of interest, namely adalimumab and dexamethasone, data extraction was limited to patients randomised to treatment arms with doses consistent with their licensed indications. Extracted information for each study included the study name (when reported), first author with publication year, characteristics of study population, interventions, comparators and outcomes. Where multiple publications of the same study were identified, data was extracted and reported as a single study.

5.1.5 Quality Assessment

The methodological quality of each included study was using an adapted Cochrane Risk of Bias tool.[53]. Quality assessment was undertaken by one reviewer (EP or KC) and checked by a second reviewer (KC or EP).

5.1.6 Data synthesis

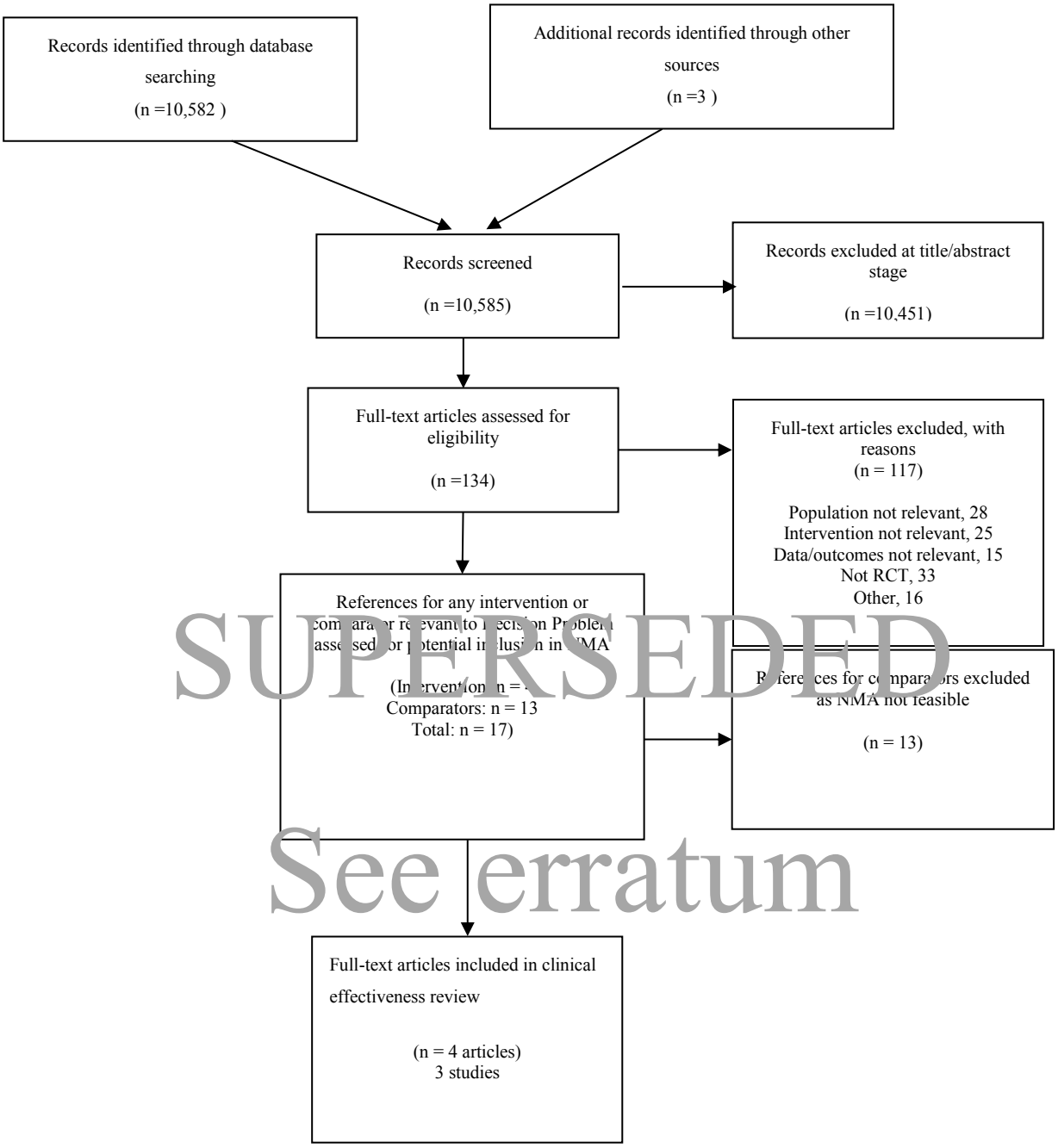
It was initially anticipated that in order to compare the interventions of interest with each other and with current standard care, pairwise meta-analyses and/or NMA may be undertaken, depending on the availability of relevant RCTs with common comparators reporting consistent outcomes. However, conducting pairwise meta-analyses or NMA was not possible for reasons presented in Section 5.3.3. Data from studies contributing to the review were therefore summarised and presented as tabular and narrative syntheses. Summary statistics e.g. mean difference between treatments for continuous outcomes and relative risks for binary outcomes, were calculated if not reported in study reports.

5.2 Results for clinical effectiveness

5.2.1 Quantity and quality of research available

Literature searches retrieved 10,585 records (10,582 from database searches and 3 from reference lists). A total of 10,451 records were excluded at title and abstract stage. Of the 134 full text articles obtained for detailed examination, 117 articles were excluded because they did not meet the eligibility criteria for the review. Details of excluded full-text articles with reasons are presented in Appendix 2. Seventeen potentially relevant articles (relating to 16 studies) were retained for potential inclusion in meta-analyses; 13 studies were related to comparators within the scope of the review whilst 3 studies (4 articles) evaluated adalimumab (subsequently abbreviated as ADA) or dexamethasone intravitreal implant 0.7mg (abbreviated as DEX 700). It was not possible to include any of the 13 studies of comparators within a NMA (reasons why this was not possible, and a summary of the 13 studies, are provided in Section 5.3.3 and Table 20). This section is therefore focussed specifically on studies of DEX 700 and ADA. Selection of studies informing the clinical effectiveness review is summarised in Figure 3 below. An example data extraction form is provided in Appendix 3 and the criteria for assessment of methodological quality in Appendix 4.

Figure 3: PRISMA flow chart



5.2.2 Assessment of effectiveness

5.2.2.1 Study characteristics

The characteristics of the two included studies of ADA and one study of DEX 700 in patients with non-infectious uveitis are summarised in Table 4.

Two studies, VISUAL I[4] (n=223 patients) and VISUAL II[5] (n=229 patients) compared ADA administered subcutaneously as a 80 mg loading dose, then 40mg repeated every other week, with a corresponding placebo treatment in patients with active (VISUAL I)[4] or inactive (VISUAL II)[5] non-

infectious intermediate, posterior or panuveitis. The treatment and follow-up period was up to 80 weeks (18 months) or until treatment failure.

One study, HURON[7] (n=229 patients), a 26-week Phase 3 trial, evaluated the effectiveness of two different dosages of DEX intravitreal implants, 0.7mg (DEX 700) and 0.35mg (DEX 350) compared to a sham procedure in patients with active, chronic non-infectious intermediate and posterior uveitis. Only data relating to the licensed DEX 700 arm are included in this review.

All three studies were international, multicentre RCTs conducted in regions including Europe, North America and Australia. VISUAL I[4] and VISUAL II[5] also included a sub-population of patients from Japan (n=16 patients and 12 patients, respectively); however, the Japanese patients were not included in the data reported in the study publications or company submission.[7, 47, 54]

Table 4: Summary of study characteristics of VISUAL I, VISUAL II and HURON

Study, Company Study dates Setting	Population: Sample size / Mean age/ % Females / Type of uveitis	Population: Diagnosis	Intervention Comparator	Prior Treatments	Concomitant treatments	Outcomes	Reference(s)
VISUAL I [NCT01138657] [4, 55] AbbVie August 2010 to August 2014 67 sites, 18 countries[a]	223[b]/ 42.7 years/ 57% (217 analysed) Active uveitis[c] Int 22%; post 33%; pan 45% Bilateral 91%; Unilateral 9% Duration, months: mean (SD): Intervention arm: 40.2 (51.3) Comparator arm: 51.0 (72.2)	Idiopathic, 37% (81/217) Sarcoid, 8% (n=18/217) Behcet's, 7% (n=16/217) VKH, 12% (n = 25/217) Birdshot chorioretinopathy, 20% (n=44/217) Multifocal choroiditis and panuveitis, 5% (11/217) Other, 10% (22/217)	Adalimumab subcutaneous injection 80 mg loading dose followed by 40 mg doses every other week Placebo	All patients: High dose oral corticosteroids	ALL: Oral prednisone 60 mg/d tapered to 0 mg by week 15. PRN: Topical corticosteroids, discontinued by week 9. Immunosuppressant (max 1) - Azathioprine: 4% (n=8/217) - Cyclosporine: 6% (n=13/217) - Mycophenolate mofetil or similar: 12% (n=25/217) - Methotrexate: 10% (n=21/217)	Primary outcome: TTF (worsening of ≥1 of: AC grade; VH grade; BCVA; or inflammatory retinal or chorioretinal vascular lesions) at/after Wk6, ≥1 eye Secondary outcomes: • BCVA (logMAR) • Change VH or AC grade • % change in CRT • Time to MO • Change in VFQ-25 • Adverse events	Jaffe 2016[56]
VISUAL II [NCT01124838] [5, 55] AbbVie August 2010 to May 2015 72 sites, 22 countries[d]	229[e]/ 42.5 years/ 61% (226 analysed) [redacted] patients from the UK Inactive uveitis[f] Int 21%; post 33%; pan 46% Bilateral, 96%; Unilateral, 4% Duration, months: mean (SD): Intervention arm: 59.5 (64.5) Comparator arm: 62.9 (67.7)	Idiopathic, 31% (n=69/226) Sarcoid, 14% (n=32/226) Behcet's, 7% (n=16/226) VKH, 23% (n = 51/226) Birdshot chorioretinopathy, 13% (n=30/226) Multifocal choroiditis and panuveitis, 3% (7/226) Other, 9% (21/226)	Adalimumab subcutaneous injection 80 mg loading dose followed by 40 mg doses every other week Placebo	All patients: High dose oral corticosteroids	ALL: Oral prednisone 10 to 35mg/d tapered to 0 mg by week 19 or earlier PRN: Topical corticosteroids, discontinued by week 9. Immunosuppressant (max. 1) - Azathioprine: 6% (n=14/226) - Cyclosporine: 12% (n=26/226) - Mycophenolate mofetil or similar: 15% (n=34/226) - Methotrexate: 15% (n=33/226)	Primary outcome: TTF (presence of ≥1 of: AC grade; VH grade; BVCA; or inflammatory retinal or chorioretinal vascular lesions) on/after Wk2, ≥1 eye Secondary outcomes: • BCVA (logMAR) • Change in VH or AC grade • % change in CRT • Time to MO • Change in VFQ-25 • Adverse events	Nguyen 2016[57]

[a] Patients included in a sub-study in Japan (n = 16, 7 sites) were excluded from the analyses of outcomes in this study due to regional heterogeneity.
[b] 217 patients analysed as ITT population.
[c] Active uveitis was characterised by the presence of VH score ≥2; and/or AC cell grade ≥2 and/or active inflammatory chorioretinal or retinal vascular lesions whilst on oral corticosteroids (10 to 60 mg/ day) for at least 2 weeks.
[d] Patients included in a sub-study in Japan (n = 32, 10 sites) were excluded from the analyses of outcomes in this study.
[e] 226 patients reported in AbbVie submission.
[f] Inactive uveitis was defined as AC cell or a vitreous haze grade≤ 0·5+, without evidence of active inflammatory chorioretinal or retinal vascular lesions and receiving 10–35 mg/day oral prednisone to maintain inactivity, observed 28 days to study entry.

Study, Company Study dates Setting	Population: Sample size / Mean age/ % Females / Type of uveitis	Population: Diagnosis	Intervention Comparator	Prior Treatments	Concomitant treatments	Outcomes	Reference(s)
HURON [NCT003338] [7, 58] Allergan May 2006 to October 2008 46 sites, 18 countries	229[g]/ 44.8 years/ 63.3% (153 of analysed sample included) Active uveitis Int 81%; post 19% Bilateral (NR); Unilateral (NR) Duration, months: mean (SD): Intervention arm[h]: 50.5 (54.2) Comparator arm: : 61.2 (62.5)	None specified (no patients had uncontrolled systemic conditions)	Single dose, dexamethasone intravitreal implant, 0.7 mg or 0.35 mg Sham injection	All patients: none specified Systemic immunosuppressant or anti-inflammatory treatment at baseline 25% (n=38/153)	PRN (stable dose): corticosteroids (topical or systemic); immunosuppressants; topical NSAIDs. Rescue medication:[i] intravitreal/periocular steroids or systemic meds for uveitis (new or increased)	Primary outcome: % patients with VH=0, at week 8 Secondary outcomes: • % patients ≥15-letter improvement in BCVA • % patients ≥10-point improvement in VFQ-25 Score • Change in CRT	Lowder 2011[7] Lightman 2013[54]

AC, anterior chamber; CRT, central retinal thickness; MO, macular oedema; PRN, pro ra nata; SD, standard deviation; TTF, time to treatment failure; VFQ, Visual Functioning Questionnaire; VH, vitreous haze, VKH, Vogt Koyanagi Harada syndrome

[g] 153 patients in relevant groups, patients randomised to dexamethasone intravitreal implant 0.7 mg and sham procedure.

[h] Treatment received by patients in this study arm was dexamethasone intravitreal implant 0.7 mg

[i] Rescue medications were permitted if VH increased ≥1 between weeks 3 and 8 or VH was ≥1.5, between weeks 8 and 26.

a) Patient characteristics

Patients included in the HURON[7] study (mean age, 44.8 years) were slightly older than those in the VISUAL I[4] and VISUAL II [5] studies (mean age, 42.5 and 42.7 years, respectively). The proportion of women varied from 57% [4] to 63%.[7]

Inclusion criteria for patients with active uveitis in VISUAL I[4] was based on the manifestation of one or more of the following: VH score ≥2; AC cell grade ≥2 and/or active inflammatory chorioretinal or retinal vascular lesions whilst on high dose oral corticosteroids (10 to 60mg/day) for at least 2 weeks. Inactive uveitis in patients included in the VISUAL II[5] study was characterised by VH score ≤0.5 and AC cell grade ≤0.5 with no active inflammatory chorioretinal or retinal vascular lesions (that is uveitis inactivity) whilst receiving 10 to 35mg/day oral prednisone or its equivalent to maintain an inactive state of inflammation ≥28 days before study entry. Patients were considered for inclusion if control of their disease was corticosteroid-dependent, i.e. they had more than 1 uveitic flare in the past 18 months occurring within 1 month of tapering steroids. In the HURON study,[7] active intraocular inflammation was based on the presence of VH score ≥1.5+ and patients unresponsive to prior corticosteroids were excluded.[7]

Mean duration of uveitis was shorter in the active treatment arms than comparator arms across all three studies (40.2 vs. 51 months for VISUAL I,[4] 59.5 vs. 62.9 months for VISUAL II[4] and 50.5 vs. 61.2 months for HURON[7]). Intermediate uveitis was the most common site of inflammation in patients (81% of patients) in the HURON study,[7] whilst panuveitis was seen more frequently in patients in the VISUAL studies[5] (approximately 46% panuveitis versus 22% intermediate uveitis versus 33% posterior uveitis).[4] Uveitis-related systemic conditions reported for patients in the VISUAL studies[4, 5] included Behcet's disease, sarcoidosis and Vogt-Koyanagi-Harada (VHK) syndrome.[4] More patients with active uveitis had no diagnosed systemic condition (73%) compared to those with inactive uveitis (56%) in the VISUAL studies.[4, 5] Limited information about relevant co-existing systemic conditions was provided for the HURON study in the journal article, company submission or clinical study report;[7] only that no patients had uncontrolled systemic conditions.[7] Over 90% of patients in the VISUAL studies[4] presented with bilateral uveitis; outcomes in the left and right eyes were considered separately, then averaged across eyes, in the analysis of the studies' findings. Conversely in the HURON study,[7] the proportion of patients with bilateral uveitis was not reported (the AG queried this and were informed by the company that these data were not collected). In patients with bilateral uveitis, the right eye was selected for treatment. Only the study eye was analysed for relevant outcomes in this study.[7] Overall, 84% of patients received treatment in the worse-seeing eye.

b) Study treatment and follow-up

The active treatment in the HURON study[7] was a single dexamethasone intravitreal implant. The study compared the licensed dose of 0.7mg (DEX 700, n=77 patients, reported here) versus a dose of 0.35mg (DEX 350, n=76 patients, not reported here) versus a sham procedure (n=76 patients). One implant was received per patient; no repeat implants were given during the 26-week follow-up period and patients had an implant in only one eye.

The active treatment evaluated in the VISUAL studies[4] was ADA. Patient randomised to the study arms (n=111 patients and 115 patients, VISUAL I[4] and VISUAL II,[5] respectively) received a loading dose of 80mg by subcutaneous injection, and then 40mg repeated every other week.[4] A corresponding placebo was administered to patients in the comparator arms (n=112 patients and 114 patients, VISUAL I[4] and VISUAL II,[5] respectively). For patients with active uveitis,[4] visits during the study were scheduled at baseline, then at weeks 1, 4, 6 and 8. Subsequently, further visits continued every 4 weeks until the primary endpoint (treatment failure) was achieved or until completion of 80 weeks of treatment. The treatment and follow-up duration was up to 80 weeks (18 months) or until treatment failure. The median duration of treatment and follow-up in VISUAL I[4] was 19 weeks for ADA and 13 weeks for placebo. In VISUAL II,[5] median duration of treatment and follow-up was 35 weeks for ADA and 22 weeks for placebo. The longer duration for ADA in both studies was due to the fact that patients in the placebo groups met the treatment failure endpoints earlier than in the ADA groups and were taken off treatment.

c) Prior treatments and concomitant treatments

All patients in the VISUAL studies[4, 5] had previously received high dose oral corticosteroids (>10mg/day prednisone or its equivalent) prior to study entry. Within VISUAL I,[4] all patients received standardised oral prednisone 60mg/day (hereafter referred to as a steroid burst) from randomisation which was gradually tapered to 0mg by week 15 of the study. Furthermore, topical corticosteroids were permitted but were tapered and discontinued by week 9. In VISUAL II,[5] all patients were already receiving oral prednisone 10 to 35mg/day; this was tapered to 0 mg by week 19 or earlier depending on steroid dose at baseline. During the study, patients were eligible to receive at least one immunosuppressant including azathioprine, cyclosporine, mycophenolate mofetil or methotrexate, at the discretion of the study investigator(s).

Limited information on prior and concomitant treatments for uveitis was reported for the HURON study,[7] although a quarter of patients in the relevant population (DEX 700 and sham) for this review had received or were using systemic immunosuppressants or anti-inflammatory treatment at baseline (n=38/153, 25%).[7] The company did, however, provide patient level data, which showed that this was generally similar across arms, but that more patients received immunosuppressant rescue therapy in the sham arm (10.5%) than the DEX 700 arm (1.3%).

In the HURON study,[7] patients were permitted to receive different treatments at the discretion of the investigator if it was indicated. Permitted treatments before and at baseline as well as during the study included the following:[58]

- peri-operative prophylactic antibiotics (at visit prior to implantation and 3 days, post-operatively);
- intra-ocular pressure (IOP) lowering treatments (if IOP >30mmHg in the study eye);
- topical corticosteroids or NSAIDs in the study eye, (if doses remained stable ≥2 weeks before screening, were stable throughout study visits, and were anticipated to remain stable up to week 8);
- intravitreal, topical or periocular corticosteroids in the non-study eye (if inflammation occurred in the non-study eye);
- cycloplegics, (indication not specified);
- cataract surgery (if reduced VA had a limiting impact on the patients, cataract interfered with uveitis management and/ or if cataract resulted in local inflammation or glaucoma. The decision to operate was at the discretion of the investigator and patient. Delay of surgery until after week 26 was encouraged);
- systemic immunosuppressants, e.g. methotrexate, cyclosporine (if doses remained stable ≥3 months before screening, were unchanged throughout study visits, and were anticipated to remain stable up to week 8);
- systemic corticosteroids e.g. oral prednisone or equivalent (if doses remained stable and were ≤20mg/day ≥1 month before screening, were stable throughout study visits, and were anticipated to remain stable up to week 8);
- oral non-steroidal anti-inflammatory drugs (NSAIDs), (indication not specified)

Within the HURON study,[7] new treatment or previous management requiring dose escalation with systemic corticosteroids or immunosuppressants or local (intravitreal, periocular and topical corticosteroids) was only permitted if any of these interventions was administered as rescue treatment. In general, rescue anti-inflammatory treatments were permissible, if VH score increased by ≥1 unit from week 3 to the start of week 8 and if VH =1.5+ was recorded from week 8 to 26.[7] Other rescue medications included anticoagulants and surgical procedures on the study eye.[7, 58]

d) Study outcomes

Primary study endpoints were different across studies:

- In the VISUAL I[4] study of ADA for active uveitis, the primary endpoint was time to treatment failure, a composite outcome including worsening of at least one of the following in ≥1 eye

(from best state achieved following steroid burst, on or after week 6): AC cell grade; VH grade; BCVA; or new active inflammatory retinal or chorioretinal vascular lesions;

- In the VISUAL II[5] study of ADA for inactive uveitis, the primary endpoint was time to treatment failure, a composite outcome including worsening of at least one of the following in ≥1 eye (from baseline, on or after week 2): AC cell grade; VH grade; BVCA; or new active inflammatory retinal or chorioretinal vascular lesions; and
- In the HURON[7] study of DEX, the primary outcome was the proportion of patients with VH score of zero at week 8 in the study eye (outcomes were also measured up to week 26).

Reported outcomes in included studies and grading criteria for intraocular inflammation are presented in Table 5 and

Table 6.

Secondary outcomes for VISUAL I[4] (Table 5) were measured from the best state prior to week 6 (following the steroid burst), while secondary outcomes for VISUAL II[5] were measured from baseline. Secondary outcomes in VISUAL I and II were only measured up to treatment failure or study end, and since treatment failure occurred in more patients in the placebo than ADA arms, results may have been worse in the placebo arms at the point of outcome measurement. The last observation carried forward (LOCF) method used for dealing with missing data may have introduced systematic bias, as it assumes that data is missing at random, which is not the case here.

Table 5: Reported efficacy outcomes in included studies: VISUAL I, VISUAL II and HURON

Study	Outcomes		Assessment methods
VISUAL I[4]	Primary outcome (composite endpoint) Time to treatment failure at or after 6 weeks: Evidence of ≥1 of the following in ≥1 eye:		
	At 6 weeks:	After 6 weeks:	
	- AC cell grade ≥0.5+	- AC cell grade: ≥2-step increase relative to best state achieved	DIO, graded by SUN criteria
	- VH grade ≥0.5+	- VH grade: ≥2-step increase relative to best state achieved	DIO, graded by NEI/ SUN criteria
	- New active, inflammatory chorioretinal or retinal lesions compared to baseline		DIO
	- Worsening of BCVA ≥15 letters compared to best score previously observed		logMAR units using ETDRS chart

VISUAL II[5]	Primary outcome (composite endpoint) Time to treatment failure on or after 2 weeks: Evidence of ≥1 of the following in ≥1 eye:	**Assessment methods**
	- New active, inflammatory chorioretinal or retinal lesions compared to baseline	DIO
	- AC cell grade: ≥2-step increase relative to baseline	DIO, graded by SUN criteria
	- VH grade: ≥2-step increase relative to baseline	DIO, graded by NEI/ SUN criteria
	- Worsening of BCVA ≥15 letters relative to baseline	logMAR units using ETDRS chart
VISUAL I and VISUAL II[4, 5 59]	Secondary outcomes VISUAL I: From best state achieved prior to week 6 to final or early termination visit VISUAL II: From baseline to final or early termination All measured for left and right eye separately, then treatment effects averaged across eyes	**Assessment methods**
	Change in AC cell grade in each eye	DIO, graded by SUN criteria
	Change in VH score in each eye	DIO, graded by NEI/ SUN criteria
	Change in BCVA in each eye	logMAR units using ETDRS chart
	Time to develop MO in at least one eye	Assessed in patients without MO at baseline
	% change in CRT in each eye	Stratus OCT with Cirrus or Spectralis system
	Change in generic and vision-specific quality of life in each eye	EQ-5D score VFQ-25 composite score, near vision subscore, near vision subscore, ocular pain subscore
	Disease quiescence	Absence of new active inflammatory lesions with AC cell and VH grade of ≤0.5+
HURON[7, 47, 58]	Primary outcome (all in study eye only)	**Assessment methods**
	VH score = 0 at week 8	Scores consistent with published colour photographic scale
	Secondary outcomes (all in study eye only)	
	BCVA	AREDS-adapted ETDRS chart
	Central macular thickness	OCT (at least 6 scans required, at selected sites)
	Early treatment failure (Allergan CSR)	VH increase ≥ 1 units from baseline, at week 3
	Late treatment failure	VH ≥ 1.5+, at week 8 or after week 8
	Use of escape medications	Medications administered to patients with early or late treatment failure
	Patient-reported outcomes	VFQ-25 composite score and subscores

AC, anterior chamber; AREDS, Age Related Eye Disease Study Research Group; BCVA, best corrected visual acuity, CRT, central retinal thickness; DIO, dilated indirect ophthalmoscopy, EQ-5D, Euroqol-5D; ETDRS, Early Treatment Diabetic Retinopathy Study Group; HADS, Hospital Anxiety and Depression Scale; HRU, Healthcare Resource Use; OCT, optical coherence tomography, MO, macular oedema; NEI, National Eye Institute, SUN, Standardisation of Uveitis Nomenclature, VFQ-25, 25-item vision-functioning questionnaire; VH, vitreous haze, WPAI, Work Productivity and Activity Impairment questionnaire

Table 6: Grading criteria of intraocular inflammation in VISUAL I, VISUAL II and HURON

AC cell score		**VH grade**			
VISUAL I and II[4, 5, 39]		VISUAL I and II[4, 5]		HURON[7]	
Grade	Criteria /number of cells[10]	Grade	Criteria	Grade	Criteria
0	< 1	0	No evident VH;	0	No inflammation
0.5+	1 to 5	0.5+	Slight blurring of the optic disc margin because of the haze; normal striations and reflex of the nerve fibre layer cannot be visualised	+0.5	Trace inflammation (slight blurring of the optic disc margins and/or loss of the nerve fibre layer reflex)
1+	6 to 15	1+	Permits a better definition of both the optic nerve head and the retinal vessels (compared to higher grades)	+1	Mild blurring of retinal vessels and optic nerve
2+:	16 to 25	2+:	Permits better visualisation of the retinal vessels (compared to higher grades)	+2	Moderate blurring of optic nerve head
3+	26 to 50	3+	Permits the observer to see the optic nerve head, but the borders are quite blurry	+3	Marked blurring of optic nerve head
4+	> 50	4+	Optic nerve head is obscured.	+4	Optic nerve head not visible
In the HURON study, a modified grade of 1.5+ was introduced which was assessed on the basis of optic nerve head and posterior retina view obstruction > +1, but < +2.					

5.2.2.2 Assessment of methodological quality of included studies

An overview of the methodological quality of the included studies is presented in Figure 4 and Table 7. Generally, all three studies performed well against all main quality items in the Cochrane Risk of Bias Tool. Suitable methods for random sequence generation were reported across all studies. In the VISUAL studies,[4, 5] the randomisation list was remotely generated by the statistics department of the company (AbbVie). Patients were subsequently allocated to study arms by means of a voice-response or web-response system. Similar methods were used in the HURON study [7], with the company (Allergan) providing a centrally generated randomisation schedule followed by an interactive allocation procedure of study participants which was remotely managed.[7] Randomisation to study arms was

[10] Assessed according to field size of 1 mm^2 of slit beam 39. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol* 2005;140.

stratified according to prior immunosuppressant treatment in the VISUAL studies;[4, 5] conversely, randomisation was stratified according to baseline VH in the HURON study.[7] Blinding of participants and investigators was assessed as satisfactory across studies. In the VISUAL studies,[4, 5] unmasking of treatment allocation was only permitted in the event of a medical emergency. In the HURON study,[7] treatment investigators were responsible for the implantation procedure; however, outcome assessors were masked to treatment received by patients.

All studies reported pre-specified inclusion and exclusion criteria. *A priori* sample size calculations for detecting between group differences for the specified primary outcomes at a significance level of 5% indicated that 234 patients were needed to achieve a power of 90% in VISUAL I;[4] 220 patients for 80% power in VISUAL II[5] and 73 patients per study arm to achieve power of 93% (HURON).[7] Based on this, VISUAL I[4] randomised 223 patients, slightly fewer than the 234 suggested by the power calculation. Demographic and baseline characteristics between study arms were comparable for all studies with the exception of duration of uveitis which was slightly longer in the non-active comparator arms as noted above. The impact of non-study treatments options available throughout the study duration is unclear, in particular in the HURON study,[7] in which patients with worsening of intraocular inflammation following implantation procedure could receive rescue (escape) medication comprising systemic corticosteroids or immunosuppressants or topical steroids. Indications for escape medication were early treatment failure (i.e. patients with VH increase ≥1 units from baseline, at week 3) or late treatment failure (i.e. patients with VH grade, at least 1.5+, at week 8 or after week 8).

The VISUAL I and II[4, 5] studies did not include data for patients in the Japanese sub-studies in their analyses. In HURON,[7] 100% of patients were included in intention-to-treat analyses, while the analyses described as "intention-to-treat" in the VISUAL studies[4, 5] excluded 6 of 223 patients (3%) in VISUAL I[4] and 3 of 229 patients (1%) in VISUAL II[5] because of "incomplete efficacy data and compliance issues at these sites".

Figure 4: Summary of methodological quality of included studies: review authors' judgement about each quality item across included studies

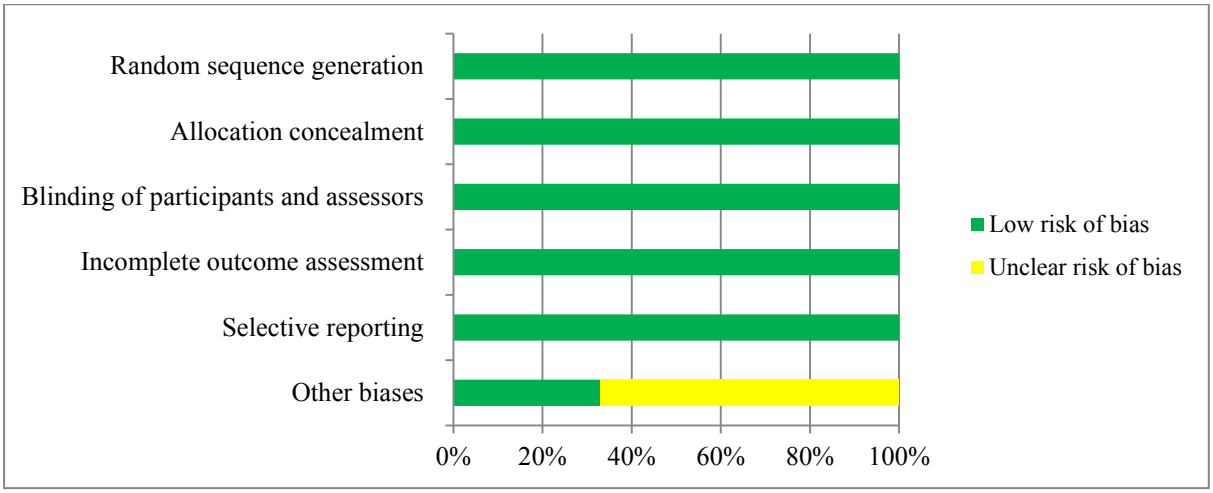


Table 7: Summary of methodological quality assessment: review authors' judgement about each methodological quality item for each study

Study	Quality assessment item								
	1	2	3	4	5	6	7	8	9
VISUAL I[4]	Y	Y	Y	N	Y	Y	Y	Y	Y
VISUAL II[5]	Y	Y	Y	Y	Y	Y	Y	Y	Y
HURON[7]	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y, yes (low risk of bias); N, no (high risk of bias); U, unclear (insufficient details to assess quality item)

1: Were participants assigned to study groups using an acceptable random method?
2: Was allocation concealment adequately conducted?
3: Were eligibility criteria specified for selecting participants?
4: Was the study adequately powered?
5: Were study groups comparable for most prognostic indicators at baseline?
6: Were patients and investigators/outcome assessors blinded to treatment allocation?
7: Was follow-up adequate (≥70% randomised patients analysed)?
8: Were reasons for attrition /exclusions stated ?
9: Was an intention-to-treat analysis included?

Feasibility of meta-analysis

It was not considered appropriate to meta-analyse the findings of the VISUAL I[4] and VISUAL II[5] studies because VISUAL I[4] enrolled patients with active uveitis and VISUAL II[5] enrolled patients with inactive uveitis. Active uveitis refers t o current inflammation in the eye, whereas patients with inactive uveitis have limited inflammation, usually because of treatment with corticosteroids or immunosuppressants. In addition, the magnitude of the treatment effect is likely to be associated with the degree of disease activity and inflammation at baseline with patients with little inflammation or vision loss at baseline less likely to show an improvement in outcome. NMA was also not considered feasible or appropriate, for the reasons discussed in Section 5.2.3.

5.2.2.3 Effectiveness results from included studies

Results for treatment failure

Treatment failure: VISUAL studies

The primary outcome for the VISUAL studies[4, 5] of ADA was a composite treatment failure outcome, defined as worsening of at least one of the following in ≥1 eye: AC cell grade; VH grade; BVCA; or new active inflammatory retinal or chorioretinal vascular lesions (Table 5). In VISUAL I,[4] outcomes were measured relative to the best state achieved following the initial steroid burst and treatment failure was assessed from week 6. In VISUAL II,[5] outcomes were measured relative to baseline and treatment failure was assessed from week 2.

In VISUAL I[4] (active uveitis), treatment failure was experienced by 54.5% of patients in the ADA arm versus 78.5% in the placebo arm (Table 8). The median time to treatment failure was 24 weeks (5.6 months) for ADA and 13 weeks (3 months) for placebo, giving a hazard ratio (HR) of 0.50 (95% CI 0.36 to 0.70, *p<0.001*). Treatment failure due to each of the four individual criteria (AC, VH, BCVA or new lesions) was also significantly greater in the placebo than ADA arm (Table 8, *p=0.04* to p<0.001).

In VISUAL II[5] (inactive uveitis), treatment failure was experienced by 39% of patients in the ADA arm versus 55% in the placebo arm (Table 8). The median time to treatment failure was not estimable for ADA (>18 months) because less than half of patients had experienced treatment failure, and 8.3 months for placebo, the HR was 0.57 (95% CI 0.39 to 0.84, *p=0.004*). Treatment failure due to reduction in BCVA was significantly greater in the placebo than ADA arm (*p=0.002*), although failure due to the other three criteria (AC, VH and new lesions) was not statistically significant (Table 8, p=*0.105* to *p=0.589*).

Treatment failure: HURON study

Treatment failure in the HURON study[7] was defined as VH grade increase ≥1 unit at week 3 to 8, or VH of at least +1.5 at week 8 to 26. No data were reported in the journal article, company submission or clinical study report, but a statistically significant difference between DEX 700 and sham (*p<0.001*) was noted.

Table 8: Summary of treatment failure outcomes reported in VISUAL I. VISUAL II and HURON

	VISUAL I[4, 55] (active uveitis)		VISUAL II[5, 55] (inactive uveitis)		HURON[7, 58] (active uveitis)	
Outcome	**ADA**	**Placebo**	**ADA**	**Placebo**	**DEX 700**	**Sham**
TF	60/110 (54.5%)[a]	84/107 (78.5%) [a]	45/115 (39%) [b]	61/111 (55%) [b]	NR [c]	NR [c]
Comparison between groups	NR		NR		p<0.001[11]	
Time to TF ≥1 eye [median/mths (IQR)],	5.6 (3.0 to not estimable)	3.0 (1.5 to 5.6)	Not estimable (4.7 to not estimable)	8.3 (3.0 to not estimable)	NR	NR
Comparison between groups HR (95% CI)	0.50 (0.36, 0.70), *p<0.001*		0.57 (0.39, 0.84), *p=0.004*		NR	
TF due to new lesions	17/110 (15.5%)	29/107 (27.1%)	NR	NR	NR	NR
Comparison between groups HR (95% CI)	0.38 (0.21, 0.69), *p=0.001*		0.55 (0.26, 1.15), *p=0.105*		NR	
TF due to AC cell grade	24/110 (21.8%)	34/107 (31.8%)	NR	NR	NR	NR
Comparison between groups HR (95% CI)	0.51 (0.30, 0.86), *p=0.01*		0.70 (0.42, 1.18), p=*0.180*		NR	
TF due to VH grade	16/110 (14.5%)	39/107 (36.4%)	NR	NR	NR	NR
Comparison between groups HR (95% CI)	0.32 (0.18, 0.58), *p<0.001*		0.79 (0.34, 1.81), *p=0.589*		NR	
TF due to reduction in BCVA	23/110 (20.9%)	27/107 (25.2%)	10/115 (9%)	23/111 (21%)	NR	NR
Comparison between groups HR (95% CI)	0.56 (0.32, 0.98), *p=0.04*		0.33 (0.16, 0.70), *p=0.002*		NR	

BCVA, best corrected visual acuity; CI, confidence interval; HR, hazard ratio; NR, not reported TF, treatment failure; VH, vitreous haze

[a]Treatment failure = at least one of: AC cell grade ≥0.5+ (at week 6) or increase ≥2 (after week 6); VH grade ≥0.5+ (at week 6) or increase ≥2 (after week 6); BVCA worsening ≥15 letters; or new active inflammatory retinal or chorioretinal vascular lesions; outcomes measured relative to best state achieved following initial steroid burst [4]

[b]Treatment failure = uveitis recurrence, defined as at least one of: AC cell grade increase ≥2; VH grade increase ≥2; BVCA worsening ≥15 letters; or new active inflammatory retinal or chorioretinal vascular lesions, on or after week 2 (relative to baseline) [5]

[c] Treatment failure = VH increase ≥1 unit at week 3 to 8 or VH of at least + 1.5 at week 8 to 26 [58]

[11] From Kaplan-Meier curve

Results for best corrected visual acuity

Best corrected visual acuity: VISUAL studies

The studies of ADA reported change in BCVA in units of logMAR (Table 9). In VISUAL I,[4] change was measured from the best state reached prior to week 6 after the initial steroid burst rather than baseline to the final value (week 80 or at time of treatment failure). BCVA improved in both the ADA and placebo arms following the initial steroid burst but worsened as time progressed, with greater worsening in the placebo arm. The change in BCVA (logMAR) from "best prior to week 6" to final or early termination was 0.07 and 0.04 in the ADA arm (left and right eyes, respectively) and 0.12 and 0.13 in the placebo arm (left and right eyes, respectively). The mean difference between groups in BCVA change, pooled across left and right eyes, was -0.07 (95% CI -0.11 to - 0.02; *p=0.003*).

In VISUAL II,[5] change was measured from baseline to the final value (week 80 or at treatment failure). BCVA stayed fairly constant from baseline to final value in the ADA arm and worsened in the placebo arm (Table 9). The change in BCVA (logMAR) from baseline to final or early termination was 0.01 and -0.01 in the ADA arm (left and right eyes respectively) and 0.06 and 0.02 in the placebo arm. The mean difference between groups in BCVA change, pooled across left and right eyes, was -0.04 (95% CI -0.08 to 0.01; *p=0.096*).

Best corrected visual acuity (BCVA): HURON study

In HURON,[7] BCVA was measured as the proportion of patients with change of ≥2 or ≥3 ETDRS lines over the 26 weeks (Table 10). The proportion with improvement ≥3 lines was 43% for DEX 700 versus 7% for sham at week 8 (*p<0.001*) and 38% for DEX 700 versus 13% for sham at week 26 (*p<0.001*). Improvement ≥2 lines followed a similar pattern (Table 10).

Table 9: Visual acuity outcomes (logMAR) reported in VISUAL I and VISUAL II - LOCF analysis[50, 60]

	VISUAL I[4] (active uveitis)				VISUAL II[5] (inactive uveitis)			
Best-corrected visual acuity: logMAR (SD)	**ADA**		**Placebo**		**ADA**		**Placebo**	
	Left eye (n=101)	Right eye (n=101)	Left eye (n=103)	Right eye (n=103)	Left eye (n=115)	Right eye (n=115)	Left eye (n=110)	Right eye (n=110)
Mean VA Baseline	0.22 (0.344)	0.23 (0.277)	0.24 (0.291)	0.25 (0.307)	0.14 (0.255)	0.12 (0.222)	0.16 (0.287)	0.15 (0.274)
Comparison between groups	NR				NR			
Mean VA Best value prior to week 6 following steroid burst (used as "baseline" for changes in VISUAL I)[4]	0.13 (0.290)	0.14 (0.243)	0.12 (0.262)	0.14 (0.271)	N/A	N/A	N/A	N/A
Comparison between groups	NR							
Mean VA Final (week 80) or early termination	0.20 (0.370)	0.18 (0.294)	0.24 (0.319)	0.27 (0.442)	0.15 (0.338)	0.11 (0.282)	0.22 (0.388)	0.16 (0.293)
Comparison between groups	NR				NR			
Mean change in VA VISUAL I[4]: From best state reached prior tow 6 to final or early termination VISUAL II[5]: From baseline to final or early termination	0.07 (0.160)	0.04 (0.143)	0.12 (0.169)	0.13 (0.320)	0.01 (0.251)	-0.01 (0.165)	0.06 (0.239)	0.02 (0.198)
Comparison between groups (pooled across left and right eyes) [Mean difference (95% CI)]	-0.07 (-0.11 to - 0.02);*p*=0.003				-0.04 (-0.08 to 0.01);*p*=0.096			
CI, confidence interval; LOCF, last observation carried forward; N/A, not applicable; NR, not reported; VA, visual acuity Values are based on analyses using last observation (LOCF) data.								

Table 10: Visual acuity outcomes reported in HURON - percentage of patients with BCVA according to Early Treatment Diabetic Retinopathy Study lines[7, 47]

HURON[7] **(active uveitis)**		
	DEX 700	**Sham**
Patients with BCVA improvement ≥3 ETDRS lines (≥15 letters): % (number of patients)		
Week 8	42.9 (33/77)	6.6 (5/76)
Mean difference (95% CI), *p-value* Relative risk (95% CI), *p-value*	36.3% (24 to 49), $p<0.001$ 6.5 (2.7 to 15.8), $p<0.001$	
Week 26	37.7 (29/77)	13.2 (10/76)
Mean difference (95% CI), *p-value* Relative risk (95% CI), *p-value*	24.5 (11 to 38), $p<0.001$ 2.9 (1.5 to 5.5), $p<0.001$	
Patients with BCVA improvement ≥2 ETDRS lines (≥10 letters): % (number of patients)		
Week 8	60 (46/77) [a]	17 (13/76) [a]
Mean difference (95% CI), p-value Relative risk (95% CI), *p-value*	43 (29 to 56), $p<0.001$ 3.5 (2.1 to 5.9), $p<0.001$	
Week 26	55 (42/77) [a]	25 (19/76)[a]
Mean difference (95% CI), *p-value* Relative risk (95% CI), *p-value*	30 (15 to 44) , $p<0.001$ 2.2 (1.4 to 3.4), $p<0.001$	
[a]Read off Figure 4 in company's submission [47] BCVA, best corrected visual acuity; CI, confidence interval, ETDRS, Early Treatment Diabetic Retinopathy Study;		

Results for patient-reported outcome measures (PROMs)

Data on PROMs derived from the publications and submission related to the VISUAL and HURON studies are reported here. These data are presented in this report before additional clinical outcomes due to their importance for the cost-effectiveness modelling.

PROMS: VISUAL studies

The main patient-reported outcome measure (PROM) reported in the journal articles for the VISUAL studies[4, 5] was VFQ-25. Additional PROMS reported in the company's submission and Clinical Study Report for VISUAL included EQ-5D, Hospital Anxiety and Depression Scale (HADS), the Work Productivity and Activity Impairment (WPAI) questionnaire and Healthcare Resource Use (HRU).

VFQ-25scores: VISUAL studies

The VFQ-25 is made up of 25 questions that cover 11 vision-specific quality of life subscales and 1 general health item.[61] Condition-specific subscales covered in the tool include general vision, distance activities, near activities, vision-specific dependency, vision-specific role difficulties, vision-specific social functioning, vision-specific mental health, driving, peripheral vision and colour vision. Responses to items in each subscale are coded and scored from 0 to 100. Summary scores for each subscale are derived from an average of scores for items within the relevant subscale. A composite score is obtained by calculating the average of all the scores from the 11 vision-specific subscales. The general health item score and blank items within the instrument are excluded when calculating the composite score. Higher scores indicate better visual functioning.

In VISUAL I,[4] ADA produced a statistically significant and clinically meaningful improvement of 4.2 points in VFQ composite score for patients with active uveitis relative to patients in the placebo arm (p=0.01) as shown in

Table 11. Of the three subscales predefined as secondary outcomes in the VISUAL studies, statistically significant and clinically meaningful differences favouring ADA over placebo were observed for changes in the near vision subscale (mean difference, 5.12; 95% CI 0.34 to 9.90; p=0.036) and the ocular pain subscale (mean difference, 10.02; 95% CI 4.86 to 15.19; p<0.001), while changes in the distance vision subscale were not statistically significant (mean difference, 1.86; 95% CI -2.03 to 5.75; p=0.346).

Table 11: Change in VFQ scores in VISUAL I[4]

Change in VFQ scores: mean (SD)		VISUAL I[4]			
	Time point	Placebo (n=102)	ADA (n=101)	Difference (95% CI)	p value
Composite score	Baseline	77.18 (17.17)	75.79 (18.26)	4.20 (1.02, 7.38)	0.010
	Change	-5.50 (11.97)	-1.30 (10.98)		
Distance vision subscale	Baseline	77.33 (20.43)	75.91 (22.25)	1.86 (-2.03, 5.75)	0.346
	Change	-5.64 (14.65)	-3.77 (13.41)		
Near vision subscale	Baseline	76.92 (19.46)	74.79 (23.53)	5.12 (0.34, 9.90)	0.036
	Change	-8.09 (17.75)	-2.97 (16.78)		
Ocular pain subscale	Baseline	84.07 (16.42)	83.66 (18.26	10.02 (4.86, 15.19)	<0.001
	Change	-12.62 (21.44)	-2.6 (15.34)		

Source: AbbVie submission Table 14 : Ranked VRQOL secondary end-points in VISUAL I[62]

In VISUAL II,[5] differences between ADA and placebo were not statistically significant for changes in VFQ-25 composite score or for the distance vision, near vision or ocular pain subscales (p=0.16 to p=0.97; Table 12).

Table 12: Change in VFQ scores in VISUAL II[5]

Change in VFQ scores: mean (SD)	VISUAL II[5]			
	Placebo (n=109)	ADA (n=115)	Difference (95% CI)	p value
Composite score	1·24 (10·7)	3·36 (11·7)	2·12 (–0·84, 5·08)	0.16
Distance vision subscale	0·76 (16·3)	2·64 (17·2)	1·88 (–2·53, 6·29)	0.40
Near vision subscale	3·98 (17·4)	3·88 (18·3)	–0·10 (–4·81, 4·61)	0.97
Ocular pain subscale	2·87 (17·2)	3·42 (21·3)	0·56 (–4·56, 5·68)	0.83

Other patient-reported outcome measures: VISUAL studies

Patient-reported outcomes reported in the company's submission and Clinical Study Report for patients in the VISUAL studies included estimates of the EQ-5D, Hospital Anxiety and Depression Scale (HADS), the Work Productivity Index (WPAI) and Hospital Resource Utilisation (HRU).

In VISUAL I, EQ-5D estimates were higher in ADA-treated patients compared to those in the placebo group (Table 13). Reported EQ-5D predicted value, assessed from change in best state achieved before week 6 to final visit or early termination demonstrated statistical significance, favouring ADA over placebo (mean difference, 0.04, p=0.044).[50, 55] Compared to patients treated with placebo, those receiving ADA missed less time off work according to estimates based on the WPAI (mean difference -10.61 days, p=0.011). There were no significant differences between treatment groups for the remaining outcomes.[50, 55]

For patients in the VISUAL II, ADA-treated patients showed a statistically significant improvement in the general vision subscore of the VFQ-25 (6.46; 95%CI, 2.28 to 10.65) and the mental health subscore (5.55; 95%CI, 0.79 to 10.30).[55] No other significant differences were reported for the other outcomes.

Table 13: EQ-5D outcomes reported in VISUAL I and VISUAL II

EQ-5D scores								
Absolute values	**VISUAL I[50]**				**VISUAL II[60]**			
	ADA (n=101)		**Placebo (n=100)**		**ADA (n=115)**		**Placebo (n=108)**	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline	[redacted]							
Best value prior to week 6	[redacted]							
Final termination	[redacted]							
Change from baseline	NR	NR	NR	NR	-0.01	0.134	-0.01	0.161
Comparison between groups, mean difference (95%CI)	NR				0.00 (-0.03 to 0.04), p =0.836			
Change from best value prior to week 6	-0.04	0.129	-0.07	0.135	NR	NR	NR	NR
Comparison between groups, mean difference (95%CI)	0.04 (0.00 to 0.07), p=0.044				NR			
CI, confidence interval; NR, not reported, SD, standard deviation Predicted values based in last observation carried forward (LOCF) in the intention-to-treat population								

VFQ-25 scores: HURON study

Table 14 is a summary of VFQ composite scores at baseline and weeks 8 and 26 reported in the HURON study.[7] At baseline, mean composite VFQ-25 scores were 63.7 (SD, 20.74) for patients in the DEX 700 group, and 71.3 (SD, 18.98) for patients in the sham group. [47]

By week 8 (based on analyses using raw scores for patients available at each time-point), the change from baseline in composite VFQ-25 score in the DEX 700 group was 11.62 points (SD 14.7) compared with 3.42 points (SD 11.1) for patients in the sham group ($p<0.001$).[58] Change at week 8 using LOCF analyses was 9.6 for DEX 700 and 4.2 for sham (SDs not reported, $p=0.007$).[54] Changes at week 26 were 10.1 versus 2.8 for patients in the DEX 700 and sham groups, respectively ($p=0.001$).

Statistically significant differences between DEX 700 and sham for changes in distance vision ($p=0.023$); near vision ($p=0.031$); peripheral vision ($p=0.045$) and vision-specific social functioning ($p=0.019$) were reported at the primary time-point (week 8) as shown in Table 14.[47,54]

Table 14: Change in VFQ scores in HURON - LOCF and per protocol (PP) population[47, 54, 58]

	HURON (active uveitis)[7]											
VFQ composite score	**Absolute values**						**Change from baseline**					
	DEX 700			**Sham**			**DEX 700**			**Sham**		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline*	73	63.7	20.74	73	71.3	18.99	NR	NR	NR	NR	NR	NR
Week 8 LOCF *	73	75.1	NR	74	74.2	NR	73	9.6	NR	74	4.2	NR
Week 8 PP	69	74.4	17.3	70	74.5	18.1	69	11.6	14.7	69	3.4	11.2
Week 16 LOCF*	73	75.9	NR	74	75.3	NR	NR	NR	NR	NR	NR	NR
Week 16 PP	69	75.3	18.12	70	75.6	19.06	69	10.47	14.28	69	4.45	12.73
Week 26 LOCF *	73	76.2	NR	74	73.2	NR	73	10.1	NR	74	2.8	NR
Week 26 or early exit (CSR)	72	74.56	19.32	73	74.27	20.40	72	10.34	16.71	72	2.84	13.86

*Estimated from graph.[54] LOCF, last observation carried forward, N, number, NR, not reported, PP, per protocol, SD, standard deviation, VFQ, Visual Function Questionnaire

Patients treated with DEX 700 were reported to have experienced greater improvements in vision-related health-related quality of life assessed by the VFQ-25 changes. More patients in the DEX 700 group compared to the sham group had a 5-point (60.9% versus 29.0%, respectively) and 10-point (50.7% versus 15.9%, respectively) improvement in composite scores.[47, 58] At weeks 8 and 26, statistically significant differences between those treated with DEX 700 implant and sham were reported for the percentage of patients with more than 5-point (week 8, $p<0.001$; week 26, $p<0.05$) or 10-point (week 8, $p<0.001$; week 26, *p*-value, reported as significant but no value given) increase in VFQ-25 scores (Table 15).[47, 58]

Other patient-reported outcome measures: HURON study

HURON presented EQ-5D (US tariff), SF-6D and SF-36 estimates at baseline, but not beyond this and no other outcomes were reported.[47,58]

Table 15: VFQ-25 score according to percentage of patients with >5-point or 10-point increase in HURON

VFQ-25 score		
	DEX 700	**Sham**
% patients with ≥5 point increase	Week 8:54.8% Week 16: NR Week 26: 57.5%	Week 8: 27.0% Week 16: NR Week 26: 32.4%
Comparison between groups	Week 8: $p<0.001$ Week 16: *p*=significant (NR) Week 26: $p<0.05$	
% patients with ≥10 point increase	Week 8: 45.2% Week 16: NR Week 26: NR	Week 8: 14.9% Week 16: NR Week 26: NR
Comparison between groups	Week 8: p<0.001 Week 16: *p*=significant (NR) Week 26: *p*=significant (NR)	
N, number, NR, not reported, VFQ, Visual Function Questionnaire		

Results of vitreous haze grade

VH was measured by dilated indirect ophthalmoscopy in both VISUAL[4, 5] and HURON[7] both cases grading was based on the original scale proposed by Nussenblatt[38] and later SUN[13] (with the minor modification of 'trace' being replaced by 0.5+ in the ordinal

difference however was that HURON[7] proposed an additional 1.5+ grade for cases to lie between the 1+ and 2+ grades. This is summarised in

Table 6 and presented in Section 5.2.2.3.

Vitreous haze grade: VISUAL studies

In the VISUAL studies,[4, 5] VH outcomes were considered as criteria contributing to the primary composite endpoints of treatment failure. In VISUAL I,[4] VH was assessed as change from the best achieved score following a mandatory steroid burst until the final or early termination visit. In VISUAL II,[5] VH was assessed as change from baseline to the final or early termination visit. Higher scores are correlated with increased severity of uveitis.

A statistically significant difference for change in VH score was reported for patients in the ADA group versus the placebo arm in the VISUAL I study [4] (-0.27, 95% CI -0.43 to -0.11, p<0.001, Table 16). Lower mean VH scores were also noted for the ADA versus placebo arm in VISUAL II,[5] but differences were not statistically significant (-0.13, 95% CI -0.28 to 0.01; p =0.070). In VISUAL I (active uveitis),[4] VH worsening was the least common cause of treatment failure in the ADA group (15% of events) and the most common reason for treatment failure in the placebo group (36% of events; HR 0.32; 95% CI 0.18 to 0.58; p<0.001).[4] Conversely, increases in VH grade in VISUAL II[5] were not significantly different between treatment groups and did not impact on time to treatment failure (HR=0.79; 95% CI 0.34 to 1.81; p=0.569).[5]

Table 16: Vitreous haze and anterior chamber cell grade in VISUAL studies[4, 50, 55, 60]

	VISUAL I[4] (active uveitis)				VISUAL II[5] (inactive uveitis)			
	ADA		Placebo		ADA		Placebo	
	Left eye (n=101)	Right eye (n=101)	Left eye (n=103)	Right eye (n=103)	Left eye (n=115)	Right eye (n=115)	Left eye (n=110)	Right eye (n=110)
VH score: mean (SD) Baseline	1.09 (0.927)	1.03 (0.812)	0.95 (0.775)	1.05 (0.865)	0.16 (0.235)	0.14 (0.225)	0.14 (0.228)	0.15 (0.230)
Comparison between groups	NR							
VH score: mean (SD) Best value prior to week 6 following steroid burst (used as "baseline" for changes in VISUAL I[4])	0.33 (0.544)	0.34 (0.425)	0.40 (0.459)	0.33 (0.412)	NA	NA	NA	NA
Comparison between groups	NR							
VH score: mean (SD) Final (Week 80) or early termination	0.44 (0.736)	0.47 (SD 0.636)	0.73 (0.795)	0.78 (0.865)	0.32 (0.594)	0.32 (0.601)	0.48 (0.728)	0.42 (0.630)
Comparison between groups	NR							
Mean change in VH (SD) VISUAL I[4]: From best state reached prior to week 6 to final or early termination VISUAL II: From baseline to final or early termination	0.11 (0.559)	0.13 (0.648)	0.33 (0.666)	0.45 (0.781)	0.16 (0.601)	0.18 (0.604)	0.33 (0.733)	0.27 (0.605)
Comparison between groups[a] [Mean difference (95% CI)]	-0.27 (-0.43 to -0.11); p<0.001				-0.13 (-0.28 to 0.01); p =0.070			
AC cell grade: mean (SD)	ADA		Placebo		ADA		Placebo	
	NR		NR		NR		NR	
Comparison between groups*	-0.29; 95% CI -0.51 to -0.07; p=0.011				-0.14; 95% CI -0.37 to 0.08; p=0.218			

* From best state reached prior to week 6 to final or early termination

LOCF, last observation carried forward; N/A, not applicable; SD, standard deviation; VA, visual acuity , VH, vitreous haze

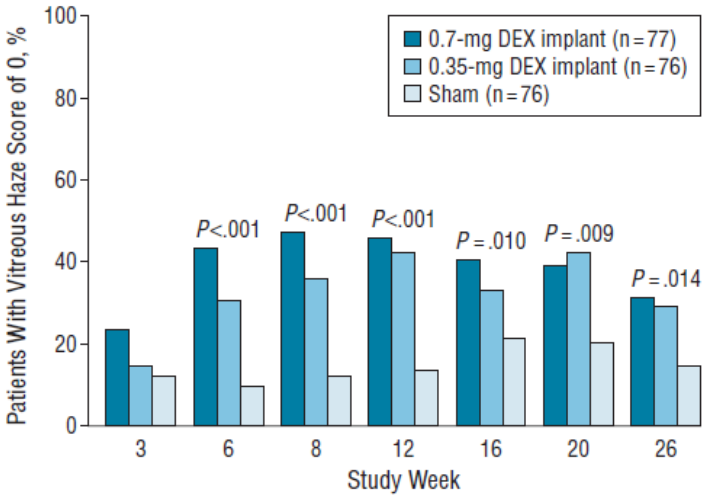
Vitreous haze grade: HURON study

Study entry eligibility included among others, a VH score of at least +1.5. At baseline, more patients had a VH score of +1.5 to +2 (84%, n = 65/77 patients and 87%, n=66/76 patients; DEX 700 and sham, respectively) than had a score of +3 to +4 (16%, n=12/77 patients and 13%, n=10/76 patients; DEX 700 and sham, respectively). Patients were stratified using these two VH cut-offs. The primary efficacy outcome was the proportion of patients with VH score of zero. Analysis was based on an ITT population and the primary time-point was week 8 following implantation; outcomes were also measured up to week 26.

Proportion of eyes achieving vitreous haze of zero: HURON study

Compared with patients receiving a sham procedure, a statistically significantly higher proportion of patients in the DEX 700 arm achieved VH score of zero at week 8 (mean difference, 34.9%, 95% CI 22% to 48%, p<0.001) and week 26 (mean difference, 16.7%, 95% CI 4% to 30%, p=0.014) (Table 17). Statistically significant treatment response was evident as early as week 6 following DEX 700 implant procedure as shown in Figure 5.

Figure 5: Patients with vitreous haze score of zero (all patients) in HURON



Source: Lowder 2011[7]

In patients with VH score of +1.5 or +2 at baseline, the proportion of eyes achieving a VH score of zero was significantly greater at week 8 (p<0.001) and week 26 (p=0.006) for patients in the DEX 700 arm compared to the sham arm (Table 17). The proportion of patients with VH of zero was also greater for DEX 700 versus sham for those patients with a score +3 or +4 at baseline, but the differences were not statistically significant (p-values not reported).

Subgroup analyses were also conducted based on previous systemic corticosteroid and/or immunosuppressant use. Differences between study arms remained statistically significant for patients with or without prior systemic therapy at week 8 and week 26 ($p<0.001$ and $p=0.001$, respectively). At study completion (week 26), differences between study arms were statistically significant for patients with no prior systemic therapy ($p\leq0.05$) but were not significant for patients with prior therapy ($p\geq0.12$, Table 17).

Table 17: Vitreous haze outcomes in HURON (ITT population)

HURON[7] (active uveitis)	**DEX 700**	**Sham**	Mean difference (95% CI), p-value Relative risk (95% CI), p-value
VH score = 0: % (number of patients)			
Week 8: All patients	46.8 (36/77)	11.8 (9/76)	MD: 34.9 (22 to 48), $p<0.001$ RR: 4.0 (2.0 to 7.6), $p<0.001$
Week 26: All patients	31.2 (24/77)	14.5 (11/76)	MD: 16.7 (4 to 30), $p=0.014$ RR: 2.2 (1.1 to 4.1), $p=0.02$
Week 8: Subgroups for baseline VH - VH +1.5 or +2 - VH +3 or +4	48.4 (31/64) 41.7 (5/12)	12.1% (8/66) 10.0 (1/10)	MD: 36 (22 to 51), $p<0.001$ RR: 4.0 (2.0 to 8.0), $p<0.001$ MD: 32 (-2 to 65), $p=0.06$ RR: 4.2 (0.6 to 30.1), $p=0.16$
Week 26: Subgroups for prior treatment - Prior systemic therapy: - No prior systemic therapy:	28.6 (4/14) 31.7 (20/63)	7.1 (1/14) 16.1 (10/62)	MD: 21 (-6 to 49), $p=0.12$ RR: 4.0 (0.5 to 31.5), $p=0.19$ MD: 16 (1 to 30), $p=0.04$ RR: 2.0 (1.0 to 3.9), $p=0.05$
Improvement ≥1 in VH score: % (number of patients)			
Week 8	94.8 (73/77)	44.7 (34/76)	MD: 50.1 (38 to 62), $p<0.001$ RR: 2.1 (1.6 to 2.7), $p<0.001$
Week 26	81.8 (63/77)	51.3 (39/76)	MD: 30.5 (16 to 45), $p<0.001$ RR: 1.6 (1.3 to 2.0), $p<0.001$
Improvement ≥2 in VH score: % (number of patients)			
Week 8	44.2 (34/77)	13% (10/76) approx[a]	MD: 31 approx, $p<0.001$ RR: 3.4 approx, $p<0.001$
Week 26	33.8 (26/77)	14% (11/76) approx[a]	MD: 19 approx, $p=0.001$ RR: 2.3 approx, $p=0.008$
Mean VH score (SD)			
Week 8	0.47 (NR)	1.44 (NR)	MD: -0.97, $p<0.001$
Week 26	0.72 (NR)	1.30 (NR)	MD: -0.58, $p<0.001$
Time to VH score = 0			
Cumulative response rate	NR	NR	NR, $p<0.001$

[a]Estimated from graph in Lowder 2011

approx.., approximately; CI, confidence interval; VH, vitreous haze; MD, mean difference, NR, not reported, RR, relative risk

Other reported outcomes related to vitreous haze: HURON study

A number of outcomes reflecting treatment response in the vitreous were reported in HURON. These secondary efficacy outcomes included mean VH score, change in VH score, improvement in VH score of ≥1 unit or ≥2 units (all measured at weeks 8 and 26), and time to VH of zero (Table 17). Analyses were undertaken using the ITT population with LOCF for efficacy outcomes following the administration of rescue treatment to patients.[7]

Time to vitreous haze of zero: HURON study

Time to VH of zero was measured from day 0 (day of implantation) to the first event of VH of zero. Time-points considered included week 3, 6, 8, or any unplanned visit or early exit from study, before week 8. Decrease in VH score to zero occurred earlier and was of a greater magnitude in effect in patients who received DEX 700 compared with those in the sham arm ($p<0.001$). [7]

Mean vitreous haze score and change in vitreous haze score: HURON study

VH scores for each study eye were assessed at each study visit. Mean VH scores were significantly lower in the DEX 700 group compared with the sham arm at week 8 and week 26 ($p<0.001$, Table 17). The proportion of patients with improvement in VH score of ≥1 unit was significantly greater for DEX 700 than sham, ($p<0.001$ throughout the study), as was the proportion with an improvement of ≥2 units (at week 3, $p = 0.023$ and from week 6 to 26, $p \leq 0.002$; DEX 700 versus sham respectively, (Table 17).[7]

Results for anterior chamber cell grade

Anterior chamber cell grade: VISUAL studies

In VISUAL I,[4] AC cell grade (see

Table 6 for criteria) worsened to a greater extent in the placebo group than the ADA group (mean difference -0.29; 95% CI -0.51 to -0.07; p=0.011). In VISUAL II[5] (patients with inactive uveitis), no significant difference in worsening of AC cell grade was noted between patients in the ADA group and the placebo arm (mean difference -0.14; 95% CI -0.37 to 0.08; p=0.218)

Anterior chamber cell grade: HURON study

In HURON,[7] the difference in the percentage of patients with 1 or more cells in the AC was statistically significant between the DEX 700 and sham arms (14.5% versus 38.7%; p=0.002 between all three groups).

Disease quiescence: VISUAL studies

In the VISUAL studies [4, 5] intraocular inflammation (assessed by VH grade and AC cell grade) was used to define disease quiescence and steroid-free quiescence as outlined below [59].

Disease quiescence

- No new active inflammatory lesions
- AC cell grade of ≤0.5
- VH grade of ≤0.5+

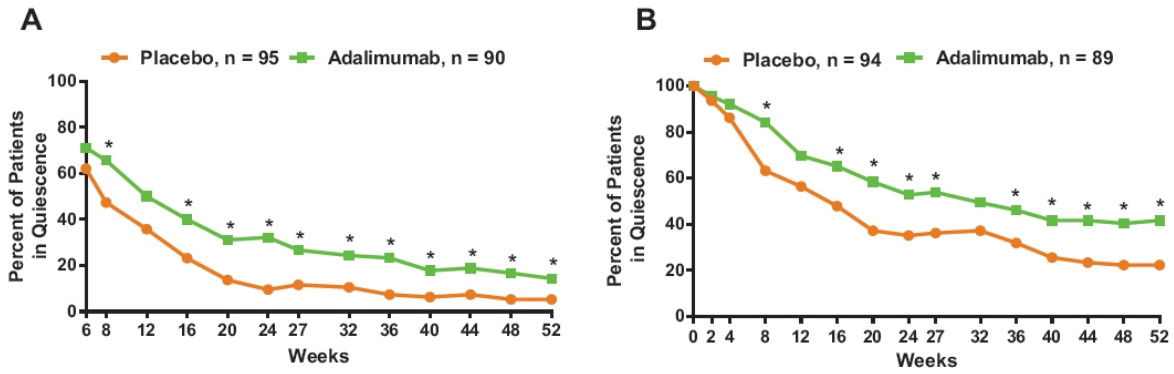
Steroid-free quiescence (when not receiving steroid therapy)

- No active inflammatory lesions
- AC cell grade of zero
- VH grade of zero

In both studies, a statistically significant higher proportion (p-values, not available) of patients in the ADA group were reported to have experienced disease quiescence and steroid-free quiescence at all assessment time points except at weeks 6 and 12 in VISUAL I and at week 16 in VISUAL II (see Figure 6 and

Figure 7).

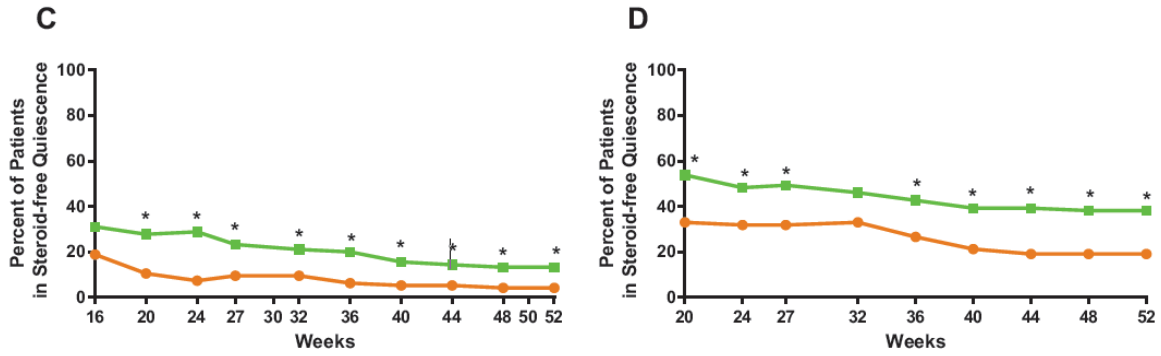
Figure 6: Proportion of patients with quiescence in VISUAL I (A) and VISUAL II studies (B)



A: In VISUAL I, treatment failure was assessed from week 6.
B: In VISUAL II, treatment failure was measured from week 2 in patients with inactive uveitis. Therefore, all patients experienced quiescence at week 0

Source: Landewee *et al.,* 2016[59]

Figure 7: Proportion of patients with steroid-free quiescence in VISUAL I (C) and VISUAL II studies (D)



C: Week 16 was the first time-point for assessing steroid-free quiescence in VISUAL I because the mandatory steroid burst was tapered to zero by week 15.
D: Week 20 was the first time-point for assessing steroid-free quiescence in VISUAL II because the mandatory steroid burst was tapered to zero by week 19

Source: Landewee *et al.,* 2016[59]

Results for macular oedema

Measures of macular oedema were reported in terms of change in central macular thickness (CMT) for patients with MO at baseline and time to OCT evidence of MO in patients who developed the condition during the studies.

Macular oedema: VISUAL studies

In the VISUAL studies,[4, 5] ADA did not significantly reduce the time to OCT evidence of MO in the patients with active uveitis (HR 0.70; 95% CI 0.39 to 1.26; *p*=0.231) or in patients with inactive uveitis (HR 0.75; 95% CI 0.34 to 1.69; p=0.491). There was a significant difference in change in CMT in patients with active uveitis (VISUAL I,[4] *p*=0.020) but not in those with inactive uveitis (VISUAL II,[5] p = 0.451) (Table 18).

Macular oedema: HURON study

CMT was assessed by optical coherence tomography (OCT) at a number of study sites in HURON. Baseline mean central macular thickness was 344.0 (SD, 141.6) µm in 39 patients in the DEX 700 group) and 324.6 (SD,145.5) µm in 43 patients in the sham group. Mean difference for the decrease in CMT between patients in the DEX 700 and sham arms was statistically significant at week 8 only (decrease -99.4 µm (SD, 151.8) versus -12.4 µm (SD, 123.7); *p*=0.004, Table 18) but not at week 26 (p=0.58).

Outcomes of incidence of MO are discussed further in Section 5.2.2.4 Safety of included interventions.

Table 18: Macular oedema outcomes in VISUAL I and VISUAL II

Macular oedema outcomes in VISUAL studies[4, 5]					
Time to macular oedema in ≤1 eye [median/ months (IQR)][a]	**ADA**		**Placebo**		Comparison between groups [HR (95%CI)]
VISUAL I [4] (active uveitis) Time frame: on or after week 6 (months)	11.1 (2.6 to 15.9) (n = 55 patients)		6.2 (1.4 to not estimable) (n = 45 patients)		0.70 (0.39 to 1.26); p=0.231
VISUAL II[5] (inactive uveitis) Time frame: on or after week 2 (months)	not estimable due to low number of events (n = 90 patients)		not estimable due to low number of events (n = 95 patients)		0.75 (0.34 to 1.69); p=0.491
Percentage change in macular thickness, µm (SD)	**ADA**		**Placebo**		Comparison between groups mean difference (95%CI)]
VISUAL I [4] (active uveitis)	Left eye	9.6 (29.76)	Left eye	20.2 (32.01)	- 11.4 (-20.9 to -1.8); p= 0.020[b]
	Right eye	8.2 (25.8)	Right eye	22.0 (32.48)	
	(n=101 patients)		(n=102 patients)		
VISUAL II[5] (inactive uveitis)	Left eye	4.5 (29.82)	Left eye	6.4 (20.67)	- 2.3 (-8.5 to 3.8); p=0.451
	Right eye	5.4 (34.83)	Right eye	7.7 (28.88)	
	(n=114 patients)		(n=107 patients)		

Macular oedema outcomes in HURON study[7]			
Decrease in macular thickness, µm (SD)	**DEX 700 (n =39 patients)**	**Sham (n=43 patients)**	**Comparison between groups [mean difference (95%CI)]**
Week 8	-99.4 (151.8)	-12.4 (123.7)	-87.0 (-147 to -27), p=0.004
Week 26	-50.2 (102.9)	-35.5 (134.9)	-14.7 (-66 to 37), p=0.58

ADA, adalimumab; CI, confidence interval; NR, not reported; SD, standard deviation,

[a] Comparison: Change from best state reached prior to week 6 to final or early termination[55]

5.2.2.4 Effectiveness data from non-randomised studies of dexamethasone

A summary of effectiveness data from 11 non-randomised, non-comparative studies of DEX 700 implant is shown in Appendix 5.[22, 48, 49, 63-70] This is based on data within the company submission for dexamethasone;[47] original study publications have not been examined due to time constraints. These data are included here as they provide some data on repeat implants, implants in both eyes and corticosteroid reduction, which were not assessed in the HURON RCT. Non-randomised studies of ADA are not included here as they were not provided in the company submission and it was beyond the scope of this assessment to undertake a *de novo* review of these data.

Following a single implant, two studies reported significant improvements in BCVA at 2 to 3 months but a return to baseline values by 6 months,[22, 66] and significant improvements in VH up to 6 months,[22,

[66] with a return to baseline by 12 months in the study with longer follow-up.[22] Significant improvements in CRT were reported up to 6 months after single implant in one study,[66] and up to 3 months in another study with a return to baseline by 6 months.[67]

Studies in which patients received between 1 and 4 implants reported improvements in BCVA at 12 months,[48, 67, 70] stated as significant in one study.[48] In studies with patients having a mix of single or multiple implants and macular oedema, significant improvements in CRT were reported up to 12 months in one study[48] while another study reported significant improvements at 3 months but not at 6 months.[69]

In terms of repeat implants, one study reported that after the second implant BCVA significantly improved by 1 month but then decreased, with a similar trend following up to 6 implants (not significant but small patient numbers).[22] CRT also showed a significant temporary improvement after the second implant with similar (non-significant) improvements after third and fourth implants, while VH showed a similar pattern.[22] Another study reported that the improvements in BCVA and CRT at 1 month were similar (not significantly different) following the first and second implants.[68]

The median time from first to second implant was 10 months in a study of uveitis patients,[48] while in four studies of uveitic macular oedema the mean/median time to second implant was 4.7, 5.0, 7.1 and 10 months.[49, 65, 67, 70] The mean time from second to third implant was 5.4 months in one study of uveitic macular oedema.[65]

Implants in both eyes were assessed in one study, in which 3/11 (27%) patients receiving implants in both eyes had a response (reduced CRT and improved BVCA) in the second eye.[22]

In terms of reduction in other therapies following a single implant, one study reported that 21/27 (78%) patients reduced or stopped systemic or local treatment,[22] while in another study 3/12 (25%) patients reduced their corticosteroid dose,[63] and in another study systemic corticosteroids were reduced or discontinued in 14/32 (44%) and discontinued in 8/32 (25%) at 6 months.[66] In studies using a mix of single or multiple implants, in one study 62% had reduction in systemic corticosteroids or immunosuppressants and 36% had steroid discontinuation at 12 months,[48] while in another study systemic corticosteroids were reduced or discontinued in 78% and discontinued in 32% at 12 months.[49]

5.2.2.5 Safety of included interventions

Safety information from Summaries of Product Characteristics

The SmPC for the dexamethasone implant states that the most commonly-reported adverse events (AEs) are those frequently observed with ophthalmic steroid treatment or intravitreal injections, including: elevated intraocular pressure (IOP); cataract; and conjunctival or vitreal haemorrhage. Less frequently reported, but more serious, adverse reactions include endophthalmitis (severe eye infection), necrotizing retinitis (viral infection of the retina), retinal detachment and retinal tear.[6]

The SmPC for ADA summarises AEs from studies of 9,506 patients across a range of conditions. The SmPC states that the most commonly reported adverse reactions are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache and musculoskeletal pain. TNF-antagonists such as ADA affect the immune system and their use may affect the body's defence against infection and cancer. Fatal and life-threatening infections (including sepsis, opportunistic infections and tuberculosis), hepatitis B virus reactivation, and various malignancies (including leukaemia, lymphoma and hepatosplenic T-cell lymphoma) have also been reported with use of ADA. Serious haematological, neurological and autoimmune reactions have also been reported, including rare reports of pancytopenia, aplastic anaemia, central and peripheral demyelinating events and reports of lupus, lupus-related conditions and Stevens-Johnson syndrome.[3]

Safety data from pivotal RCTs

Safety data from the RCTs are based on the published journal articles for HURON[7] and VISUAL I and II,[4, 5] the company submissions [47, 55] and clinical study reports.[50, 58, 60] In the case of HURON, the safety data are based on all patients who were randomised to a group and received treatment: 76/77 (99%) for the DEX 700 group and 75/76 (99%) for the sham group. Within the 26-week trial, the mean exposure to the intervention was 25.9 weeks in both the DEX 700 and sham groups. For the two RCTs of ADA versus placebo, safety data included all randomised patients in both trials: n=111 (100%, ADA) and 112 (100%, placebo) in VISUAL I, and 115 (100%, ADA) and 114 (100%, placebo) in VISUAL II. It should be noted that in these trials, exposure to ADA was longer than exposure to placebo because treatment failure (and cessation of study treatment) occurred earlier; median exposure in VISUAL I was 19 weeks (ADA) versus 13 weeks (placebo), and in VISUAL II was 35 weeks (ADA) versus 22 weeks (placebo). Therefore, one may expect more events in the ADA than placebo groups.

A summary of adverse events (AEs) is provided in Table 19. An AE of any type occurred in 80% (DEX 700) versus 68% (sham) in HURON,[7] and in 85-91% (ADA) versus 79-84% (placebo) in the two VISUAL studies.[4, 5] Serious AEs occurred in 9% (DEX 700) versus 8% (sham) in HURON, and in 6-14% (ADA) versus 5-8% (placebo) in the VISUAL studies.[4, 57] There were no deaths in the HURON study,[7] and one death in the ADA arms of each of the VISUAL studies;[4, 57] neither death was considered to be treatment-related.

Systemic AEs

Serious systemic AEs are shown in Table 20. Table 21 lists other systemic AEs which either a) occurred in at least 5% of patients in any treatment group (for HURON[7]), or b) occurred in at least 5% of patients in the ADA groups (for the VISUAL trials),[4, 71] and/or c) were noted as potentially important within uveitis treatments by clinical advisors to the AG. No reported systemic AEs (serious or non-serious) were substantially higher for DEX 700 compared with sham. Serious infections were higher for ADA than placebo in VISUAL I[4] (4.5% versus 1.8%) but not VISUAL II[5] (1.7% versus 1.8%). Malignancies and chronic renal failure each occurred in a total 3 patients across the ADA arms of both trials, versus no patients in the placebo arms. The majority of the listed systemic AEs were somewhat higher for ADA than placebo.

Immunogenicity

In VISUAL I,[4] anti-adalimumab antibodies were detected in 3/110 (2.7%) patients in the ADA group. These 3 patients had treatment failure at 16, 44 and 48 weeks (compared with a median time to treatment failure of 24 weeks among the remaining 107 patients).[4] In VISUAL II,[5] anti-adalimumab antibodies were detected in 6/115 (5%) patients in the ADA group. Five of these six patients had treatment failure at weeks 13, 16, 16, 24 and 31 (not estimable for the remaining patients).[5]

Ocular AEs

Ocular AEs are shown in Table 22. In terms of serious ocular AEs, endophthalmitis (severe eye infection) and severe uveitis worsening occurred in 1 patient each in the DEX 700 group versus none for placebo. Conjunctival haemorrhage occurred in 30% for DEX 700 versus 21% for sham, while rates were low in the VISUAL trials. Other ocular AEs are detailed in Table 22.

Raised IOP occurred in 25% for DEX 700 versus 7% for sham, while there was little difference between ADA and placebo. In the DEX 700 group, IOP ≥25 mmHg peaked at Week 3 (7.1% versus 1.4% placebo), while IOP ≥35 mmHg peaked at Week 12 (4.1% versus 0% placebo). By Week 26, no patients in the DEX 700 group had IOP ≥25 mmHg, versus 4.2% in the placebo group.

Glaucoma rates showed little difference between DEX 700 (0%) and sham (2.7%) in HURON or between ADA (0.9%) and placebo (0%) in VISUAL I.[4] In HURON, no patients required incisional surgery for glaucoma, while 2 patients (2.6%) in the DEX 700 group required laser iridotomies in the study eye for iris bombe and raised IOP. At any single time-point across the 26 weeks, up to 23% of patients in the DEX 700 group required IOP-lowering medication (the percentage requiring this at any point in the study is not reported).

Cataracts occurring among eyes that were phakic (had a natural lens) at baseline were 9/62 (15%) for DEX 700 versus 4/55 (7%) for sham. Cataracts occurring among phakic eyes with no cataract at baseline were 9/42 (21%) for DEX 700 versus 4/28 (14%) for sham. For ADA, no data were reported on whether eyes were phakic or had cataract at baseline; cataracts occurring in all patients were higher for ADA than placebo in VISUAL I[4] (3.6% versus 1.8%) but higher for placebo in VISUAL II[5] (1.7% versus 5.3%). Cataract surgery among phakic eyes occurred in 1/62 (1.6%) for DEX 700 versus 2/55 (3.6%) for sham; in VISUAL II[5] cataract surgery occurred in 1 patient for ADA versus 2 patients for placebo.

Safety data from non-randomised studies of dexamethasone

A summary of safety data from 11 non-randomised, non-comparative studies of dexamethasone implant is shown in Appendix 6.[22, 48, 49, 63-70] This is based on data presented within the company submission for dexamethasone.[47] The proportion of patients with increased IOP is typically higher in real-world studies than in an RCT, which may reflect the inclusion of patients with prior need for IOP-lowering medications, who were excluded from HURON.[47] Implant migration to the AC has been reported in a few patients and occurred in eyes which were aphakic (no lens) or pseudophakic (artificial lens).[47] A few cases of endophthalmitis or retinal detachment were reported after administration of DEX 700.[47] Non-randomised studies of ADA are not included here as they were not provided in the company submission and it was beyond the scope of this assessment to undertake a *de novo* review of these data.

Table 19: Summary of adverse events in included RCTs

Trial	HURON		VISUAL I[4](active uveitis)		VISUAL II[5] (inactive uveitis)	
Intervention / comparator	**DEX implant 0.70mg**	**Sham**	**ADA, 40mg every 2wk**	**Placebo**	**ADA, 40mg every 2wk**	**Placebo**
Time over which AEs measured	26 wk (mean 25.9 wk)	26 wk (mean 25.9 wk)	≤80 wk (median 19 wk)	≤80 wk (median 13 wk)	≤80 wk (median 35 wk)	≤80 wk (median 22 wk)
AEs (all)	61/76 (80.3%)	51/75 (68.0%)	94/111 (84.7%)	88/112 (78.6%)	105/115 (91.3%)	96/114 (84.2%)
AEs considered possibly treatment-related	46/76 (60.5%)	21/75 (28.0%)	ADA-related: 45/111 (40.5%) Steroid-related: 57/111 (51.4%)	ADA-related: 35/112 (31.3%) Steroid-related: 53/112 (47.3%)	ADA-related: 64/115 (55.7%) Steroid-related: 50/115 (43.5%)	ADA-related: 52/114 (45.6%) Steroid-related: 48/114 (42.1%)
Serious AEs	7/76 (9.21%)	6/75 (8.0%)	15/111 (13.5%)	5/112 (4.5%)	7/115 (6.1%)	9/114 (7.9%)
Serious AEs considered possibly treatment-related	NR	NR	ADA-related: 6/111 (5.4%) Steroid-related: 2/111 (1.8%)	ADA-related: 2/112 (1.8%) Steroid-related: 2/112 (1.8%)	ADA-related: 2/115 (1.7%) Steroid-related: 0/115 (0%)	ADA-related: 2/114 (1.8%) Steroid-related: 3/114 (2.6%)
Discontinuations due to AEs	2/76 (2.6%)	0/75 (0%)	11/111 (9.9%)	4/112 (3.6%)	10/115 (8.7%)	7/114 (6.1%)

AE, adverse effect, wk, week

Table 20: Serious systemic adverse events (all those reported in RCTs)

Trial	HURON[7]		VISUAL I[4] (active uveitis)		VISUAL II (inactive uveitis)	
Intervention / comparator	**DEX implant 0.70mg**	**Sham**	**ADA, 40mg every 2wk**	**Placebo**	**ADA, 40mg every 2wk**	**Placebo**
Deaths	0/76 (0%)	0/75 (0%)	1/111 (0.9%) (not treatment-related)	0/112 (0%)	1/115 (0.9%) (not treatment-related)	0/114 (0%)
Hospitalisation	NR	NR	NR	NR	NR	NR
Infections (serious)	NR	NR	5/111 (4.5%)	2/112 (1.8%)	2/115 (1.7%)	2/114 (1.8%)
Tumours/malignancy	NR	NR	2/111 (1.8%)	0/112 (0%)	1/115 (0.9%)	0/114 (0%)
Anaphylactic reaction	NR	NR	1/111 (0.9%)	0/112 (0%)	NR	NR
Demyelinating disease	NR	NR	1/111 (0.9%)	0/112 (0%)	0/115 (0%)	0/114 (0%)
Renal failure, chronic	NR	NR	1/111 (0.9%)	0/112 (0%)	2/115 (1.7%)	0/114 (0%)
Accidental overdose	NR	NR	1/111 (0.9%)	0/112 (0%)	NR	NR
Ligament/tendon rupture	NR	NR	1/111 (0.9%)	0/112 (0%)	NR	NR
Fracture	NR	NR	0/111 (0%)	1/112 (0.9%)	1/115 (0.9%)	1/114 (0.9%)
Hepatitis, acute	NR	NR	0/111 (0%)	1/112 (0.9%)	NR	NR
Abortion induced	NR	NR	0/111 (0%)	1/112 (0.9%)	NR	NR
Neutropenia	NR	NR	NR	NR	1/115 (0.9%)	0/114 (0%)
Dysphagia (difficulty swallowing)	NR	NR	NR	NR	1/115 (0.9%)	0/114 (0%)
Dysarthria (unclear speech)	NR	NR	NR	NR	1/115 (0.9%)	0/114 (0%)
Status migrainosus	NR	NR	NR	NR	1/115 (0.9%)	0/114 (0%)
Epistaxis (nosebleed)	NR	NR	NR	NR	1/115 (0.9%)	0/114 (0%)
Pleurisy	NR	NR	NR	NR	1/115 (0.9%)	0/114 (0%)
Cardiac tamponade	NR	NR	NR	NR	1/115 (0.9%)	0/114 (0%)
Aortic dissection	NR	NR	NR	NR	1/115 (0.9%)	0/114 (0%)
Deep vein thrombosis	NR	NR	NR	NR	0/115 (0%)	2/114 (1.8%)
Hypertensive crisis	NR	NR	NR	NR	0/115 (0%)	1/114 (0.9%)
Arthritis	NR	NR	NR	NR	0/115 (0%)	1/114 (0.9%)
Cerebrovascular accident	1/76 (1.3%)	0/75 (0%)	NR	NR	NR	NR
Pelvic inflammatory disease	1/76 (1.3%)	0/75 (0%)	NR	NR	NR	NR
Cerebellar infarction	1/76 (1.3%)	0/75 (0%)	NR	NR	NR	NR
Pyelonephritis	0/76 (0%)	1/75 (1.3%)	NR	NR	NR	NR
Ankylosing spondylitis	0/76 (0%)	1/75 (1.3%)	NR	NR	NR	NR

Table 21: Systemic adverse events in RCTs

Trial	HURON[7]		VISUAL I[4] (active uveitis)		VISUAL II[5] (inactive uveitis)	
Intervention / comparator	**DEX 700**	**Sham**	**ADA, 40mg every 2wk**	**Placebo**	**ADA, 40mg every 2wk**	**Placebo**
Systemic AEs (≥5% in any group for DEX or ≥5% in treatment group for ADA)						
Nasopharyngitis	NR		21/111 (18.9%)	8/112 (7.1%)	18/115 (15.7%)	19/114 (16.7%)
Headache	5/76 (6.6%)	5/75 (6.7%)	12/111 (10.8%)	15/112 (13.4%)	17/115 (14.8%)	17/114 (14.9%)
Fatigue	0/76 (0%)	2/75 (2.7%)	12/111 (10.8%)	7/112 (6.3%)	14/115 (12.2%)	9/114 (7.9%)
Arthralgia (joint pain)	0/76 (0%)	2/75 (2.7%)	10/111 (9.0%)	11/112 (9.8%)	27/115 (23.5%)	12/114 (10.5%)
Back pain	NR	NR	9/111 (8.1%)	2/112 (1.8%)	9/115 (7.8%)	7/114 (6.1%)
Injection site reactions	NR	NR	7/111 (6.3%)	7/112 (6.3%)	23/115 (20.0%)	15/114 (13.2%)
Urinary tract infection	NR	NR	7/111 (6.3%)	0/112 (0%)	13/115 (11.3%)	10/114 (8.8%)
Cough	NR	NR	7/111 (6.3%)	4/112 (3.6%)	11/115 (9.6%)	6/114 (5.3%)
Bronchitis	NR	NR	7/111 (6.3%)	4/112 (3.6%)	NR	NR
Hyperhidrosis (increased sweating)	NR	NR	7/111 (6.3%)	3/112 (2.7%)	NR	NR
Muscle spasms	NR	NR	7/111 (6.3%)	4/112 (3.6%)	NR	NR
Nausea	0/76 (0%)	4/75 (5.3%)	6/111 (5.4%)	7/112 (6.3%)	2/115 (1.7%)	3/114 (2.6%)
Paraesthesia ("pins + needles")	NR	NR	6/111 (5.4%)	0/112 (0%)		
Insomnia	NR	NR	5/111 (4.5%)	8/112 (7.1%)	8/115 (7.0%)	3/114 (2.6%)
Myalgia (muscle pain)	NR	NR	5/111 (4.5%)	2/112 (1.8%)	6/115 (5.2%)	2/114 (1.8%)
Hypertension	2/76 (2.6%)	3/75 (4.0%)	4/111 (3.6%)	1/112 (0.9%)	7/115 (6.1%)	5/114 (4.4%)
Liver changes: Alanine aminotransferase increased	NR	NR	1/111 (0.9%)	2/112 (1.8%)	8/115 (7.0%)	1/114 (0.9%)
Liver changes: Aspartate aminotransferase increased	NR	NR	1/111 (0.9%)	1/112 (0.9%)	6/115 (5.2%)	1/114 (0.9%)
Pain in extremity	NR	NR	NR	NR	10/115 (8.7%)	3/114 (2.6%)
Upper respiratory tract infection	NR	NR	NR	NR	10/115 (8.7%)	3/114 (2.6%)
Injection site pain	NR	NR	NR	NR	8/115 (7.0%)	9/114 (7.9%)
Sinusitis	NR	NR	NR	NR	8/115 (7.0%)	4/114 (3.5%)
Additional systemic AEs (noted as potentially important by clinical advisors)						
Anxiety	NR	NR	5/111 (4.5%)	0/112 (0%)	5/115 (4.3%)	2/114 (1.8%)
Renal: Elevated creatinine	NR	NR	4/111 (3.6%)	2/112 (1.8%)	2/115 (1.7%)	3/114 (2.6%)
Weight gain	NR	NR	3/111 (2.7%)	2/112 (1.8%)	2/115 (1.7%)	0/114 (0%)
Anaemia	NR	NR	3/111 (2.7%)	0/112 (0%)	0/115 (0%)	2/114 (1.8%)

Trial	HURON[7]		VISUAL I[4] (active uveitis)		VISUAL II[5] (inactive uveitis)	
Intervention / comparator	**DEX 700**	**Sham**	**ADA, 40mg every 2wk**	**Placebo**	**ADA, 40mg every 2wk**	**Placebo**
Muscle weakness (myasthenia)	NR	NR	3/111 (2.7%)	0/112 (0%)	NR	NR
Cushing's syndrome	NR	NR	2/111 (1.8%)	1/112 (0.9%)	1/115 (0.9%)	0/114 (0%)
Depression	NR	NR	1/111 (0.9%)	1/112 (0.9%)	2/115 (1.7%)	3/114 (2.6%)
Diabetes	NR	NR	1/111 (0.9%)	2/112 (1.8%)	2/115 (1.7%)	0/114 (0%)
Osteoporosis	NR	NR	1/111 (0.9%)	1/112 (0.9%)	0/115 (0%)	2/114 (1.8%)

AE, adverse effect

Table 22: Ocular adverse events in RCTs

Trial	HURON[7]		VISUAL I[4] (active uveitis)		VISUAL II[5] (inactive uveitis)	
Intervention / comparator	**DEX 700**	**Sham**	**ADA, 40mg every 2wk**	**Placebo**	**ADA, 40mg every 2wk**	**Placebo**
Serious ocular AEs in study eye* (all reported in trials)						
Retinal detachment	2/76 (2.6%)	2/75 (2.7%)	1/111 (0.9%)	1/112 (0.9%)	0/115 (0%)	1/114 (0.9%)
Endophthalmitis (severe eye infection)	1/76 (1.3%)	0/75 (0%)	NR	NR	NR	NR
Uveitis worsening (as serious AE)	1/76 (1.3%)	0/75 (0%)	NR	NR	NR	NR
Cataract (as serious AE)	0/76 (0%)	1/75 (1.3%)	NR	NR	NR	NR
Choroidal neovascularisation	NR	NR	1/111 (0.9%)	0/112 (0%)	0/115 (0%)	1/114 (0.9%)
Transient blindness	NR	NR	NR	NR	1/115 (0.9%)	0/114 (0%)
Subretinal fluid	NR	NR	NR	NR	0/115 (0%)	1/114 (0.9%)
Ocular AEs in study eye* (≥5% in any group for DEX or ≥5% in treatment group for ADA)						
Raised IOP	19/76 (25.0%)	5/75 (6.7%)	3/111 (2.7%)	2/112 (1.8%)	3/115 (2.6%)	2/114 (1.8%)
IOP ≥25 mmHg	Wk 3: 5/70 (7.1%) Wk 8: 3/73 (4.1%) Wk 26: 0/74 (0%)	Wk 3: 1/70 (1.4%) Wk 8: 0/71 (0%) Wk 26: 3/72 (4.2%)	NR	NR	NR	NR
IOP ≥35 mmHg	Wk 3: 1/70 (1.4%) Wk 8: 2/73 (2.7%) Wk 26: 0/74 (0%)	Wk 3: 0/70 (0%) Wk 8: 0/71 (0%) Wk 26: 0/72 (0%)	NR	NR	NR	NR
Conjunctival haemorrhage	23/76 (30.3%)	16/75 (21.3%)	0/111 (0%)	1/112 (0.9%)	3/115 (2.6%)	2/114 (1.8%)
Vitreous haemorrhage	NR	NR	Eye haemorrhage: 1/111 (0.9%) Retinal haemorrhage: 1/111 (0.9%)	Eye haemorrhage: 0/112 (0%) Retinal haemorrhage: 2/112 (1.8%)	1/115 (0.9%)	0/114 (0%)
Ocular discomfort	10/76 (13.2%)	6/75 (8.0%)				
Eye pain	9/76 (11.8%)	10/75 (13.3%)	9/111 (8.1%)	2/112 (1.8%)	9/115 (7.8%)	6/114 (5.3%)
Cataract - Of all patients - Of phakic eyes at baseline - Of phakic eyes with no cataract at baseline	 9/76 (11.8%) 9/62 (14.5%) 9/42 (21.4%)	 4/75 (5.3%) 4/55 (7.3%) 4/28 (14.3%)	 4/111 (3.6%) NR NR	 2/112 (1.8%) NR NR	 2/115 (1.7%) NR NR	 6/114 (5.3%) NR NR
Iridocyclitis	7/76 (9.2%)	4/75 (5.3%)	1/111 (0.9%)	0/112 (0%)	3/115 (2.6%)	2/114 (1.8%)
Ocular hypertension	6/76 (7.9%)	0/75 (0%)	3/111 (2.7%)	1/112 (0.9%)	0/115 (0%)	2/114 (1.8%)

Trial	HURON[7]		VISUAL I[4] (active uveitis)		VISUAL II[5] (inactive uveitis)	
Intervention / comparator	**DEX 700**	**Sham**	**ADA, 40mg every 2wk**	**Placebo**	**ADA, 40mg every 2wk**	**Placebo**
Myodesopsia (floaters or vitreal cells)	6/76 (7.9%)	5/75 (6.7%)	NR	NR	NR	NR
Uveitis / uveitis worsening	6/76 (7.9%)	7/75 (9.3%)	11/111 (9.9%)	8/112 (7.1%)	6/115 (5.2%)	9/114 (7.9%)
Conjunctival hyperaemia (red eye)	5/76 (6.6%)	7/75 (9.3%)	NR	NR	NR	NR
Vision blurred	5/76 (6.6%)	3/75 (4.0%)	8/111 (7.2%)	2/112 (1.8%)	NR	NR
Macular oedema	3/76 (3.9%)	6/75 (8.0%)	NR	NR	7/115 (6.1%)	7/114 (6.1%)
Eye pruritis (itching)	3/76 (3.9%)	5/75 (6.7%)	NR	NR		
Visual acuity reduced	1/76 (1.3%)	4/75 (5.3%)	NR	NR	6/115 (5.2%)	10/114 (8.8%)
Eye swelling	1/76 (1.3%)	4/75 (5.3%)	NR	NR	NR	NR
Conjunctivitis	0/76 (0%)	4/75 (5.3%)	NR	NR	NR	NR
Additional ocular AEs in study eye* (noted as potentially important by clinical advisors)						
Cataract surgery - Of all patients - Of phakic eyes at baseline - Of phakic eyes with no cataract at baseline	 1/76 (1.3%) 1/62 (1.6%) 1/42 (2.4%)	 2/75 (2.7%) 2/55 (3.6%) 2/28 (7.1%)	NR	NR	 1/115 (0.9%) NR NR	 2/114 (1.8%) NR NR
IOP-lowering medications	Up to 16/71 (23%) at any single time-point	NR, presumed 0%	NR	NR	NR	NR
IOP-lowering surgery - Incisional surgery, laser trabeculoplasty, cryotherapy - Laser iridotomy	 0/76 (0%) 2/76 (2.6%)	 0/75 (0%) 0/75 (0%)	NR	NR	NR	NR
Glaucoma	0/76 (0%)	2/75 (2.7%)	1/111 (0.9%)	0/112 (0%)	NR	NR
Low IOP (hypotony)	1/76 (1.3%)	0/75 (0%)	NR	NR	NR	NR

*Study eye relates to the Dex study (HURON) where one eye was designated the study eye

AE, adverse effect; IOP, intra-ocular pressure

5.2.2.6 Ongoing studies

Ongoing studies relevant to the Decision Problem are shown in Table 23. These were identified via a search of the ClinicalTrials.gov database (for terms for uveitis plus adalimumab or dexamethasone) and from the dexamethasone company submission.[47]

Ongoing studies of DEX 700

Two ongoing RCTs of DEX 700 were identified, both in patients with macular oedema due to uveitis. Both compare against other local treatments. The POINT trial (NCT02374060, due to complete 2018) compares DEX 700 versus intravitreal triamcinolone or periocular triamcinolone, while the MERIT trial (NCT02623426, due to complete 2019) compares DEX 700 versus intravitreal methotrexate or intravitreal ranibizumab. In addition, a long-term safety cohort study of DEX 700 (NCT01539577) in 875 patients with posterior segment-involving uveitis or central or branch retinal vein occlusion (CRVO or BRVO) was due to complete in March 2016, but no published results were identified.

Ongoing studies of ADA

Three ongoing RCTs of ADA were identified. One small RCT (the ADUR trial, NCT00348153)[72] compared ADA plus corticosteroids and immunosuppressants versus corticosteroids in combination with immunosuppressants, and was due to be completed in March 2013. This is potentially of interest due to its active comparator arm. However, no published results were identified other than an abstract reporting intermediate results for 20 of 25 patients; this was not included in the clinical effectiveness section due to the limited results presented.[72] Two further RCTs of ADA are due to complete in 2019. The RUBI trial (NCT02925351) aims to compare ADA against two further biologic therapies: anakinra (an interleukin-1 receptor antagonist) and tocilizumab (an antibody against the interleukin-6 receptor). The IVAS trial (NCT02706704) compares subcutaneous ADA against intravitreal ADA.

In addition, a non-randomised extension study of ADA (VISUAL III, M11-327, NCT01148225) enrolled patients from the VISUAL I and VISUAL II studies (ADA or placebo arms) who either completed these trials or experienced treatment failure. Patients who discontinued VISUAL I or II due to treatment failure were defined as having active disease at VISUAL III entry, while patients who completed VISUAL I or II had inactive disease. They received open-label ADA (40mg every other week) and were followed up for 78 weeks (active uveitis patients) or 54 weeks (inactive uveitis patients). The completion date is 2018. Preliminary data are available from a conference abstract.[73] This states that of 243 patients with active uveitis after 78 weeks, 96.3% had no new inflammatory lesions relative to week-8, 91.0% had AC cell grade ≤0.5+, and 87.8% had VH grade ≤0.5+. Of 128 patients with inactive uveitis after 54 weeks, 98.5% had no new inflammatory lesions relative to baseline, 98.5% had AC cell grade ≤0.5+, and 92.6% had VH grade ≤0.5+. Mean systemic corticosteroid daily dose decreased from 12.7 to 3.68 prednisone equivalents by year 1 for patients with active uveitis and

remained stable from 1.48 to 1.21 prednisone equivalents for inactive patients. Adverse events rates were stated to be comparable to the VISUAL I and VISUALII trials, but no data were presented in terms of number of patients with events. No data were presented for visual acuity or VFQ-25.

Table 23: Ongoing studies

Study name Company	Type N est.	Population	Interventions	Key outcomes	Follow-up	Start and end dates	Reference
DEX 700							
PeriOcular and INTravitreal Corticosteroids for Uveitic Macular Edema Trial (POINT) JHSPH Center for Clinical Trials / National Eye Institute (NEI)	RCT 267	- Non-infectious anterior, intermediate, posterior or panuveitis - Active or inactive - Macular oedema	- DEX 700 - Intravitreal triamcinolone 4 mg - Periocular triamcinolone 40 mg	- Change in CRT - IOP elevation - Change in BCVA	8 and 24 weeks	March 2015 to July 2018	ClinicalTrials.gov [NCT02374060]
Macular Edema Ranibizumab v. Intravitreal Anti-inflammatory Therapy Trial (MERIT) JHSPH Center for Clinical Trials / National Eye Institute (NEI)	RCT 240	- Non-infectious anterior, intermediate, posterior or panuveitis - Inactive or minimally active - Macular oedema	- DEX 700 - Intravitreal methotrexate 400 ug - Intravitreal ranibizumab 0.5 mg	- Change in CRT	8 weeks and 6 months	Nov 2016 to March 2019	ClinicalTrials.gov [NCT02623426]
A Long-Term Safety Study of Ozurdex in Clinical Practice Allergan	Cohort 875	- Central or branch retinal vein occlusion (CRVO or BRVO) or non-infectious posterior segment-involving uveitis - Macular oedema	- DEX 700	- Adverse events	2 years	Mar 2012 to Mar 2016 (CSR available Sept 2016*)	ClinicalTrials.gov [NCT01539577]
ADA							
Adalimumab in Uveitis Refractory to Conventional Therapy (ADUR Trial) Heidelberg University / Abbott	RCT 25	- Non-infectious uveitis - Active despite ≥7.5mg/d corticosteroids	- Adalimumab 40mg every other week + corticosteroids + immunosuppressants - Corticosteroids + immunosuppressants	- % BCVA improved ≥3 lines ETDRS - Inflammatory activity - Cystoid macula edema - Cumulative steroid dosage	Up to 24 weeks	Aug 2006 to March 2013	ClinicalTrials.gov [NCT00348153] Abstract: Mackensen 2012[72]
Randomized Trial Comparing Efficacy of Adalimumab, Anakinra and Tocilizumab in Non-infectious Refractory Uveitis (RUBI) Assistance Publique - Hôpitaux de Paris	RCT 120	- Non-infectious intermediate, posterior, or pan-uveitis - Active	- Adalimumab 40mg every other week - Anakinra 100 mg/day - Tocilizumab 162 mg/week	- % ≥2-step reduction in VH or AC cells - Change in VH - Change in BCVA - Change in CRT - Change in steroid dose	16 weeks	Oct 2016 to May 2019	ClinicalTrials.gov [NCT02929251]

Study name Company	Type N est.	Population	Interventions	Key outcomes	Follow-up	Start and end dates	Reference
Intravitreal Adalimumab Versus Subcutaneous Adalimumab in Non-infectious Uveitis (IVAS)	RCT 32	- Non-infectious intermediate, posterior, or pan-uveitis - Active	- Adalimumab (subcutaneous) 40mg every other week - Adalimumab (intravitreal), 1.5 mg/ 0.03 mL every 4 weeks	- Change in VH - Change in AC score - Change in BCVA (ETDRS, logMAR) - Change in CRT - Success in steroid tapering	26 weeks	Feb 2016 to June 2019	ClinicalTrials.gov [NCT02706704]
A Study of the Long-term Safety and Efficacy of Adalimumab in Subjects With Intermediate-, Posterior-, or Pan-uveitis (VISUAL III) AbbVie (previously Abbott)	Non-RCT 400	- Non-infectious intermediate, posterior, or pan-uveitis - Active or inactive patients from VISUAL I and VISUAL II (completed or experienced treatment failure	- Adalimumab 40mg every other week	- Adverse events - BCVA, new lesions, VH, AC cells, CRT, VFQ-25, reduction in immunosuppression (active and inactive pts separately)	Up to 330 weeks (6.3 years)	Nov 2010 to Mar 2018	ClinicalTrials.gov [NCT01148225] Abstract Suhler 2016[73]

*Allergan submission

AC, anterior chamber; BCVA, best-corrected visual acuity; CRT, central retinal thickness; EDTRS, Early Treatment Diabetic Retinopathy Study; IOP, intra-ocular pressure; logMAR, logarithm of the Minimum Angle of Resolution; N est, Number of patients estimated; RCT, randomised controlled trial; VFQ-25, Visual Functioning Questionnaire-25; VH, vitreous haze

5.2.3 Indirect comparison of treatments: rationale for not undertaking

The Decision Problem states that relevant comparators include: periocular or intravitreal corticosteroid injections; intravitreal corticosteroid implants; systemic corticosteroids; systemic immunosuppressants; TNF-alpha inhibitors; and intravitreal methotrexate. The trials of DEX 700 and ADA only compared these interventions to placebo/sham. In the absence of direct evidence comparing ADA and DEX 700, and the absence of direct evidence comparing either of these treatments to a comparator reflective of current UK practice, an indirect comparison using an NMA was considered. An NMA allows a simultaneous comparison between interventions based on a synthesis of any direct and indirect evidence about treatment effects across RCTs that share at least one treatment in common with at least one other study.

5.2.3.1 Consideration of indirect comparison for all studies of clinically relevant comparators

RCTs which included any of the treatments in the comparator decision set for posterior segment-involving uveitis were sought. In addition to the one of DEX 700 (OZURDEX)[7] and two of ADA (VISUAL I and II),[4, 5] 13 additional trials of relevant comparators were identified,[34, 35, 74-84] as shown in Table 24.

Unfortunately, it was considered infeasible and inappropriate to conduct an NMA for the reasons outlined in Table 24. However, a brief summary of all identified trials of relevant comparators is provided in this section for information: study characteristics in Table 25 and a summary of reported outcomes in Table 26 . Reasons for not including the additional identified trials in the NMA included the following:

1) No link to the network containing ADA and DEX 700 i.e. no common comparator: this applies to studies of fluocinolone implant,[74, 75] periocular steroids,[77] methotrexate[34, 84] and mycophenolate mofetil.[34] The use of elicitation of experts' belief to inform the parameters required to link disconnected networks was considered in depth but was not implemented for two reasons. It was deemed to be infeasible in the time frame and, moreover, would be of questionable benefit given the concerns related to the comparability of the two main trials (see Section 5.2.3.2) and hence the validity of the resulting connected network.
2) Heterogeneity in patient populations in terms of active/inactive uveitis: It was not considered appropriate to pool studies of patients with active and inactive uveitis. Active uveitis refers to current inflammation in the eye, whereas patients with inactive uveitis have limited inflammation, usually due to treatment with corticosteroids or immunosuppressants. The treatment effect is likely to be related to the degree of

activity/inflammation at baseline. The trial of etanercept,[78] one trial of ADA (VISUAL II),[5] and one trial of voclosporin[82, 83] could not be analysed with the HURON[7] and VISUAL I[4] studies for this reason. In terms of trials in patients with inactive uveitis, the trials of etanercept[78] and voclosporin[82, 83] had no comparable outcome data in order to conduct an NMA with VISUAL II.[5]

3) Heterogeneity in patient populations for other reasons: The trial of intravitreal triamcinolone[76] was in patients who all had uveitic macular oedema (UMO), whereas in most trials only a subset had UMO. The treatment effect is likely to be associated with the proportion of patients with UMO at baseline because UMO causes vision loss. Therefore, treating UMO is likely to lead to greater gains in vision than treating patients with uveitis but no UMO. The trial of azathioprine[79] was in patients who all had Behcet's disease, whereas most trials were in a mixed population with only a small percentage having Behcet's and other systemic diseases; again, this is a clinically very different population. In addition, as noted in Section 5.2.3.2, there are many differences in population and prior and concomitant treatments between the DEX 700 (HURON[7]) and ADA (VISUAL I[4]) studies for active uveitis.
4) Lack of comparable outcomes. Within the trials that had a common comparator with DEX 700 or ADA (i.e. a placebo arm),[76, 78-80, 82, 83] none reported outcomes consistent with those in the DEX 700 and ADA trials (outcomes summarised in Table 26). Change in VFQ-25 was reported for both HURON[7] and VISUAL I[4] but an NMA was not considered appropriate for the reasons listed in Section 5.2.3.2.

Table 24: Studies considered for network meta-analysis: Rationale for non-inclusion

Trial name /ref	HURON[7, 54]	VISUAL I[4]	VISUAL II[5]	MUST[74]	Pavesio 2010[75]	Shin 2015[76]	Ferrante 2000[77]	Foster 2003[78]
Intervention	**Dex implant** (LOCAL STEROID)	**ADA** (ANTI-TNF)	**ADA** (ANTI-TNF)	**Fluo implant** (LOCAL STEROID)	**Fluo implant** (LOCAL STEROID)	**Triam intravit inj.** (LOCAL STEROID)	**Triam perioc inj.** (LOCAL STEROID)	**Etanercept** (ANTI-TNF)
Comparator	**Placebo** (sham)	**Placebo**	**Placebo**	**Steroids & immuno.**	**Steroids & immuno.**	**Placebo** (sham)	**M-pred perioc inj.**	**Placebo**
Reasons for non-inclusion in NMA	• Outcomes measured from baseline (different to VISUAL)	• Outcomes measured from peak after steroid burst to treatment failure (not from randomisation as in HURON)	• Inactive uveitis • Outcomes measured from baseline	• Not connected to network	• Not connected to network	• 100% uveitic macular oedema • No data on VA, VH, VFQ-25	• Not connected to network	• Inactive uveitis • No comparable VA outcomes • No data on VH or VFQ-25
Trial name / ref	**Yazici 1990[79]**	**Murphy 2005[35]**	**de Vries 1990[80]**	**Nussenblatt 1991[81]**	**Bodaghi 2012 (Active)[82, 83]**	**Bodaghi 2012 (Maintenance)[82, 83]**	**Mackensen 2013[84]**	**Rathinam 2004[34]**
Intervention	**Azathioprine** (IMMUNOSUPP.)	**Cyclosporine** (IMMUNOSUPP.)	**Cyclosporine** (IMMUNOSUPP.)	**Cyclosporine** (IMMUNOSUPP.)	**Voclosporin** (IMMUNOSUPP.)	**Voclosporin** (IMMUNOSUPP.)	**Methotrexate** (IMMUNOSUPP.)	**Methotrexate** (IMMUNOSUPP.)
Comparator	**Placebo**	**Tacrolimus**	**Placebo**	**Prednisolone**	**Placebo**	**Placebo**	**Interferon-β**	**Mycophen. mofetil**
Reasons for non-inclusion in NMA	• 100% Behcet's disease • No clear data on VA, VH, VFQ-25	• Only connected via study of cyclosporine versus sham (de Vries 1990) which has no data on VA, VH, VFQ-25	• No data on VA, VH, VFQ-25	• Only connected via study of cyclosporine versus sham (de Vries 1990) which has no data on VA, VH, VFQ-25	• No data on VA, VH, VFQ-25	• Inactive uveitis • No data on VA, VH, VFQ-25	• Not connected to network	• Not connected to network

Anti-TNF, anti-tumour necrosis factor; immunosupp, immunosuppressant; NMA, network meta-analysis; VA, visual acuity; VFQ-25, Visual Functioning Questionnaire-25; VH, vitreous haze

Table 25: Studies considered for network meta-analysis: Study characteristics

Trial name Author, year	HURON[7, 54]	VISUAL I[4]	VISUAL II[5]	MUST[74]	Pavesio 2010[75]	Shin 2015[76]	Ferrante 2000[77]	Foster 2003[78]
Intervention	**DEX 700**	**ADA** (40mg every 2wk)	**ADA** (40mg every 2wk)	**Fluocinolone implant** (0.59mg)	**Fluocinolone implant** (0.59mg)	**Triamcinolone intravitreal inject.**	**Triamcinolone periocular injection**	**Etanercept** (25mg SC twice/wk)
Comparator	**Placebo** (sham)	**Placebo**	**Placebo**	**Systemic steroids & immunosuppressant**	**Systemic steroids & immunosuppressant**	**Placebo** (sham)	**Methylprednisolone periocular inject.**	**Placebo**
N pts randomised	153 (DEX 700+sham)	223	229	255	140	50	36	20
Age: inc, mean (rnge)	≥18, 45 (18 to 82)	≥18, 43 (18 to 81)	≥18, 43 (NR)	≥13, 46 (NR)	≥6, 42 (12-75)	≥20, 52 (NR)	NR, NR (NR)	≥18, 47 (NR)
Location of uveitis	Int/post	Int/post/pan	Int/post/pan	Int/post/pan	Int/post/pan	NR	Int/post	NR
Duration uveitis (mo)	Dex 51, Sham 61	Ada 40, Pbo 51	61	Fluo 47, Control 43	NR	NR	NR	NR (6mo MTX)
Bilateral uveitis (%)	NR	91%	96%	88%	NR	NR	NR	NR
% with MO	NR	36% left; 37% right	NR	41%	NR	100%	NR	NR
Systemic conditions	No uncontrolled systemic condition	None 73%, sarcoid 8%, Behcet's 7%, VKH 12%	None 56%, sarcoid 16%, Behcet's 6%, Other 8%	None 73%, systemic 27%; none requiring systemic therapy	None requiring systemic therapy	None 48%, systemic 52% (sarcoid, Behcet's, VKH)	NR	None 60%, SLE 15%, HLA-B27 15%, arthritis 10%
Current inflammation (active, non-active)	Active	Active	Inactive (≥2 wk days)	Active (or recently active)	Inactive ("clinically quiet")	NR	Active (vitritis or UMO)	Inactive
Inclusion criteria: visual acuity and inflammation	- VH ≥1.5 - BCVA 10-75 letters	At least one of: - VH ≥2 - AC cell grade ≥2 - Inflammatory lesions	- VH ≤0.5 - AC cell grade ≤0.5 - No inflammatory lesions - Steroid dependent	- No VH criteria (some had VH=0) - BCVA = hand motions or better	- VH ≤2 - AC cells ≤10 - Visual acuity ≥1.4 logMAR (6/150)	- Uveitic macular oedema - BCVA 25 to 80 EDTRS letters	- Uveitic macular oedema or vitritis	NR
% prior HD steroids / immunosuppressants	26% steroids or imm.	100% HD steroids	100% HD steroids; some imm.	Some steroids; some imm. (% NR)	100% HD steroids; none imm.	100% HD steroids; some imm.	NR	100% methotrexate (imm.)
Concomitant treatment	- 26% stable dose steroids or imm. - Rescue: local steroids, systemic meds (new or incr)	- All: Prednisone 60mg/d, tapered by wk 15 - Some imm, max 1	- All: Prednisone 30-35mg/d tapered by wk 19 - Some: imm, max 1	- Fluo arm: Steroids & imm discont. - Control arm: Steroids (tapered), imm (86%)	- Fluo arm: Steroids & imm discont. - Control arm: HD steroids +/- imm - Rescue: steroids	All: Systemic steroids or imm and topical steroids	NR	All: Methotrexate (tapered); steroid eyedrops if needed
Which eyes treated	One (right if bilat.)	N/A (systemic)	N/A (systemic)	Both if bilateral	One (worse if bilat.)	One (worse if bilat.)	NR (assume one)	N/A (systemic)
Which eyes analysed	Study eye only	Left & right sep.	Left & right sep.	All uveitic eyes	Study eye only	Study eye only	NR (study eye?)	Both eyes, all pts
Duration: treatment & follow-up	Single implant Follow-up 6 months (26 wk)	Up to 80 wk (1.5yr) Ada: 19 wk [med] Pbo: 13 wk [med]	Up to 80 wk (1.5yr) Ada: 35 wk [med] Pbo: 22 wks [med]	Repeat if recurred Follow-up 2 years	Single implant Follow-up 2 years	Repeat if MO recurred Follow-up 6 months	Repeat at 6 wk if needed Follow up 3 months	6 months (24 weeks)

(cont.)

Trial name Author, year	Yazici 1990[79]	Murphy 2005[35]	de Vries 1990[80]	Nussenblatt 1991[81]	Bodaghi 2012 (Active)[82, 83]	Bodaghi 2012 (Maintenance)[82, 83]	Mackensen 2013[84]	Rathinam 2004[34]
Intervention	**Azathioprine** (2.5mg/kg daily)	**Cyclosporine** (2.5-5.0mg/kg daily)	**Cyclosporine** (10mg/kg/d)	**Cyclosporine** (10mg/kg/d, oral)	**Voclosporin** (0.2, 0.4, 0.6 mg/kg BID)	**Voclosporin** (0.2, 0.4, 0.6 mg/kg BID)	**Methotrexate** (20mg SC weekly)	**Methotrexate** (25mg oral weekly)
Comparator	**Placebo**	**Tacrolimus** 0.03-0.08mg/kg (daily)	**Placebo**	**Prednisolone** (42-64mg/d, oral)	**Placebo**	**Placebo**	**Interferon-β**(44ug SC 3 times weekly)	**Mycophenolate mofetil** (1g twice/d)
N pts randomised	48	37	27	56	218	232	19	80
Age: inc, mean (rnge)	Any age, 32 (NR)	NR, med 43 (NR)	≥18, 45 (22-75)	≥10, 38 (10-61)	≥13, med 42 (NR)	≥13, med 43 (NR)	≥18, med 42 (NR)	≥16, 39 (NR)
Location of uveitis	NR	Int/post/pan	Int/post/pan	Int/post	Int/post/pan	Int/post/pan	Intermediate	Int/post/pan
Duration uveitis (mo)	Aza 103, Pbo 83	12-24	Cyclo 67, Pbo 78	NR	52	52	≥1 yr	NR
Bilateral uveitis (%)	71%	76%	NR	100%	NR	NR	NR	81%
% with MO	NR	NR	NR	35%	NR	NR	100%	41%
Systemic conditions	Behcet's 100%	None 70%, Behcet's 11%, sarcoidosis 8%	None 74%, Behcet's 15%, sarcoidosis 11%	None 82%, sarcoidosis 13%, VKH 5%	NR	NR	None 74%, multiple sclerosis 26%	None 35.5%, VKH 54%, Behcet's 8%, sarcoidosis 2.5%
Current inflammation (active, non-active)	NR	NR	Active	Active	Active	Inactive	Active	Active
Inclusion criteria: visual acuity and inflammation	NR	NR	- BCVA ≤0.5 in best eye (or Behcet's or trauma)	- VA 20/40 or worse, both eyes - Inflammation (VH, VA decrease, retinal lesions)	- VH ≥2	NR	- Uveitic macular oedema (≥250um) - Visual acuity ≤20/30 (0.2 logMAR)	At least one of: - VH ≥1 - AC cell grade ≥1 - Vitreous cells ≥1 - Active lesions
% prior HD steroids / immunosuppressants	No steroids or imm. (past month)	100% HD steroids (or required)	100% HD steroids	No steroids or imm. (past month)	100% HD steroids (or contra/refused)	100% HD steroids	100% HD steroids and acetazolamide	100% HD steroids
Concomitant treatment	Rescue: Systemic steroids if required	Some: Oral steroids only	All: Oral steroids (tapered)	No systemic treatments; topical meds permitted	Some: Oral steroids	Some: Oral steroids	NR	All: Oral steroids (tapered) Some: Topical steroid
Which eyes treated	N/A (systemic)	N/A (systemic)	N/A (systemic)	N/A (systemic)	N/A (systemic)	N/A (systemic)	N/A (systemic)	N/A (systemic)
Which eyes analysed	Both? (unclear)	Per patient	Unclear	Per patient	Study eye or either	Study eye or either	Study eye (worse)	All uveitic eyes
Duration: treatment & follow-up	2 years	3 months	Up to 1 year	3 months	6 months (24 wk)	6 months (26 wk)	3 months	6 months

AC, anterior chamber; aza, azathioprine; BCVA, best-corrected visual acuity; bilat, bilateral; cyclo, cyclosporine; EDTRS, Early Treatment Diabetic Retinopathy Study; fluo, fluocinolone; HD, high-dose; HLA-B27, human leukocyte antigen B27; imm, immunosuppressants; int, intermediate; logMAR, logarithm of the Minimum Angle of Resolution; med, median; mo, months; MO, macular oedema; MTX, methotrexate; N, number; N/A, not applicable; NR, not reported; pan, panuveitis; Pbo, placebo; post, posterior; sep, separately; SLE, systemic lupus erythematosus; UMO, uveitic macular oedema; VA, visual acuity; VH, vitreous haze; VKH, Vogt-Koyanagi-Harada disease; wk, weeks; yr, years

Table 26: Studies considered for network meta-analysis: Outcomes reported

Trial name /ref	HURON[7, 54]	VISUAL I[4]	VISUAL II[5]	MUST[74]	Pavesio 2010[75]	Shin 2015[76]	Ferrante 2000[77]	Foster 2003[78]
Intervention	**Dex implant**	**ADA**	**ADA**	**Fluo implant**	**Fluo implant**	**Triam intravit inj.**	**Triam perioc inj.**	**Etanercept**
Comparator	**Placebo** (sham)	**Placebo**	**Placebo**	**Steroids & immuno.**	**Steroids & immuno.**	**Placebo** (sham)	**M-pred perioc inj.**	**Placebo**
Visual acuity								
VA final value		Y (logMAR)	Y (logMAR)	Y (ETDRS): 6, 2,24m		(No data just p=NS)		
VA change	Y (ETDRS): 6m	Y (logMAR)	Y (logMAR)	Y (ETDRS): 6,12,24m				
% improved ≥3 lines	Y: 2, 6mo			Y: 24 mo	Y: 24 mo			
% improved ≥2 lines	Y: 2, 6mo						Y	Y
Inflammatory activity								
VH: final	Y (final, no SD)	Y (final & change)	Y (change)					
% VH = 0	Y	Y		Y				
% VH improved ≥1	Y							
% VH improved ≥2	Y			(HR only)				
AC cell grade: change		Y	Y					
Complications								
Cataract: Incidence	Y	Y	Y	Y	Y	Y		
Cataract: % surgery	Y		Y	Y	Y	Y		
MO incidence	Y	Y		Y				
Time to MO		Y	Y					
Macular thick: change	Y	Y	Y			(no data, p-value)		
% eyes MO improved					Y (improved)			
Steroid reduction								
% reduced steroids						Y (% reduced)		
% rescue steroids	Y (intravit/systemic)						Y (intravitreal)	
Composite outcomes								
Time to treatment failure (active uveitis)		Y (worse AC cells; VH; VA; lesions)						
Uveitis recurrence			Y: AC; VH; VA; lesion		Y (AC; VH; VA)			Y (uveitis flare-ups)
Composite (positive)								
HRQoL								
Generic HRQoL		EQ5D, HADS, WPAI		Y (EQ-5D, SF-36)				
VFQ-25 comp: final	Y: 2, 4, 6m	Y		Y: 6, 12, 24m				
VFQ-25 comp: chge	Y (no SD/SE): 2, 6m	Y	Y	Y: 6, 12, 24m				
Adverse effects								
Systemic AEs	Y	Y	Y	Y	Y			Y

Trial name /ref	HURON[7, 54]	VISUAL I[4]	VISUAL II[5]	MUST[74]	Pavesio 2010[75]	Shin 2015[76]	Ferrante 2000[77]	Foster 2003[78]
Intervention	Dex implant	ADA	ADA	Fluo implant	Fluo implant	Triam intravit inj.	Triam perioc inj.	Etanercept
Comparator	Placebo (sham)	Placebo	Placebo	Steroids & immuno.	Steroids & immuno.	Placebo (sham)	M-pred perioc inj.	Placebo
Ocular AEs	Y	Y	Y	Y	Y	Y	Y	

(cont.)

Trial name / ref	Yazici 1990[79]	Murphy 2005[35]	de Vries 1990[80]	Nussenblatt 1991[81]	Bodaghi 2012 (Active)[82, 83]	Bodaghi 2012 (Maintenance)[82, 83]	Mackensen 2013[84]	Rathinam 2004[34]
Intervention	Azathioprine	Cyclosporine	Cyclosporine	Cyclosporine	Voclosporin	Voclosporin	Methotrexate	Methotrexate
Comparator	Placebo	Tacrolimus	Placebo	Prednisolone	Placebo	Placebo	Interferon-β	Mycophen. mofetil
Visual acuity								
VA final value							Y (Snellen, logMAR)	
VA change	(unclear data)		(Landon Cyp-value)				Y (ETDRS, logMAR)	Y (logMAR)
% improved ≥3 lines				Y				
% improved ≥2 lines		Y					Y	
Inflammatory activity								
VH: final					(unclear data)		Y (final)	
% VH = 0								
% VH improved ≥1								
% VH improved ≥2				Y				
AC cell grade: change				Y			Y	
Complications								
Cataract: Incidence								Y
Cataract: % surgery								
MO incidence								
Time to MO								
Macular thick: change							Y	
% eyes MO improved				Y (resolved)			Y improved/resolved	Y (resolved)
Steroid reduction								
% reduced steroids			Y (% stopped)					
% rescue steroids	Y (intravenous)							
Composite outcomes								
Time to failure, active								
Uveitis recurrence		Y (prev responders)				Y (recurrence)		
Composite (positive)		Y: VA ≥2 lines or ophthalmoscopy=0	(no data, p-value)	Y (VA ≥3 lines or VH improvement ≥2)				Y: % steroid-sparing control inflammation
HRQoL								
Generic HRQoL							(SF-36. no data)	

Trial name / ref	Yazici 1990[79]	Murphy 2005[35]	de Vries 1990[80]	Nussenblatt 1991[81]	Bodaghi 2012 (Active)[82, 83]	Bodaghi 2012 (Maintenance)[82, 83]	Mackensen 2013[84]	Rathinam 2004[34]
Intervention	**Azathioprine**	**Cyclosporine**	**Cyclosporine**	**Cyclosporine**	**Voclosporin**	**Voclosporin**	**Methotrexate**	**Methotrexate**
Comparator	**Placebo**	**Tacrolimus**	**Placebo**	**Prednisolone**	**Placebo**	**Placebo**	**Interferon-β**	**Mycophen. mofetil**
VFQ-25 comp: final							Y	
VFQ-25 comp: chge								
Adverse effects								
Systemic AEs	Y	Y	Y	Y			Y	Y
Ocular AEs							Y	Y

AC, anterior chamber; AE, adverse effect; EDTRS, Early Treatment Diabetic Retinopathy Study; EQ5D, EuroQol-5D; fluo, fluocinolone; HADS, Hospital Anxiety and Depression Scale; HR, hazard ratio; HRQoL, health-related quality of life; immuno, immunosuppressants; logMAR, logarithm of the Minimum Angle of Resolution; mo, months; MO, macular oedema; M-pred, methylprednisolone; mycophen. mofetil, mycophenolate mofetil; VFQ-25, National Eye Institute Visual Functioning Questionnaire; NS, not significant; SD, standard deviation; SE, standard error; SF-36, Short Form-36; Triam, triamcinolone; VA, visual acuity; VH, vitreous haze; WPAI, Work Productivity and Activity Impairment questionnaire; Y, yes (reported)

5.2.3.2 Consideration of indirect comparison for trials of ADA and dexamethasone

The outcomes reported vary from trial to trial (see Section 5.2.2.1) and so the potential networks of evidence were considered separately for each outcome of interest. Outcomes considered for the NMA were VFQ-25, visual acuity, VH and adverse events. This was driven by the potential to undertake a NMA for these outcomes.

Two networks of evidence were considered. A diagram of Network 1 is provided in

Figure 8. Network 1 consists of two trials (HURON[7] and VISUAL I[4]) and allows pairwise comparison to be made between ADA, DEX 700 and placebo/sham (the common comparator of the two trials). The trials share common assessment time points at 8, 16 and 26/27 weeks (26 weeks for HURON[7] and 27 weeks for VISUAL I[4]). Given that HURON[7] is a 26 week trial comparison beyond this time point is not possible based on the obse rved data.

A diagram of Network 2 is provided in Figure 9. Network 2 is an extension of Network 1, including the Multicenter Uveitis Steroid Treatment (MUST) trial of fluocinolone corticosteroid implant versus systemic corticosteroids and immunosuppressants under the assumption that the efficacy of the fluocinolone implant is the same as that of DEX 700. This allows an indirect comparison to systemic corticosteroids and immunosuppressants which may be considered more reflective of current UK practice than placebo/sham. An indirect comparison using this network is only possible at 26 weeks (the first follow up in the MUST trial).

Figure 8: Network 1 for VFQ-25 outcome. Indirect comparison of adalimumab, dexamethasone and placebo/sham .

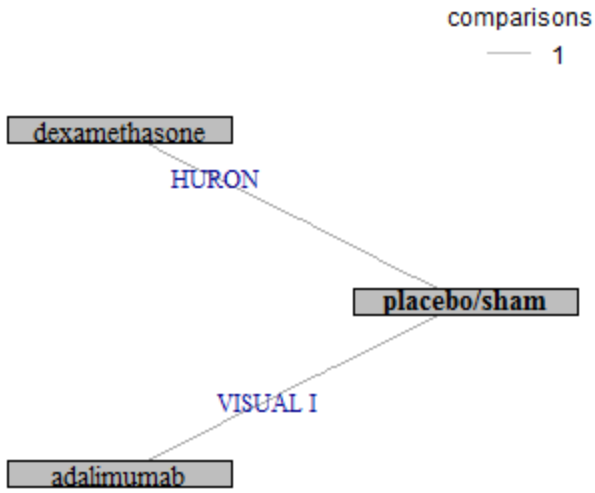
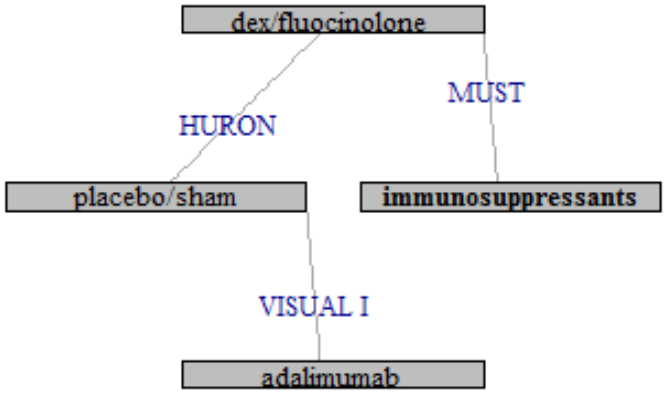


Figure 9: Network 2 for VFQ-25 outcome. Indirect comparison of adalimumab, dexamethasone, placebo/sham and immunosuppressants.



The AG began with a question about the best way to compare the treatment options within a network, with the prior belief that such an analysis could be undertaken. However, after substantial deliberation

between all members of the AG and with the clinical advisors, it was relunctantly decided that an NMA was inappropriate and may provide misleading results. The main issues are listed below.

- **Baseline systemic therapy**

  In HURON, only 26% of patients were receiving systemic therapy at baseline whereas in VISUAL I[4], all patients were receiving systemic high-dose corticosteroids. Therefore, patients in these studies may have been at different "lines" of treatment. In addition, in VISUAL I[4], 91% of patients had bilateral uveitis, whereas the corresponding proportion is not reported in the case of HURON;[7] this may be a further difference in the patient populations in these studies.

- **Rescue therapy**

  A greater proportion of patients in the sham arm in HURON[7] received rescue therapy than in the DEX 700 arm (38.2% versus 22.1%). In VISUAL I[4], there was no reported difference in concomitant therapy between the two arms. It may be misleading to attribute an indirect effect of ADA versus DEX 700 to these interventions alone.

- **Comparability of the baseline treatments in HURON and VISUAL I.[4]**

  VISUAL I included an initial steroid burst that was not included in HURON.[7] Thus, the baseline interventions are different and it would only be meaningful to combine the treatment effects across studies if the initial steroid burst did not affect the treatment effect. However, clinical advice suggests that the treatment effect will depend on the initial steroid burst. Patients experience an initial improvement from the steroid bust and there is less scope during this period for patients to demonstrate further improvement (i.e. effect of ADA is not additive to the effect of the steroids). In the analyses undertaken by the company this issue is addressed by considering the "change from peak within first 6 weeks to final/termination visit" for each individual. This approach was not considered appropriate for estimating treatment effect because patients are only comparable at baseline and treatment effects should be estimated relative to baseline.

- **Validity of comparable efficacy assumption for dexamethasone and fluocinolone (Network 2 only).**

  Although DEX 700 and fluocinolone are both corticosteroid intravitreal implants, they cannot be considered clinically equivalent because the fluocinolone implant has higher potency (median duration of effect 30 months)[85] compared to the DEX 700 implant (median duration of effect of 6 months).[47] There are no head-to-head trials comparing DEX 700 and fluocinolone implants.

- **Issues with the reported data.**

  Patients in VISUAL I[4] were followed up to the time of treatment failure only and missing data beyond this point was imputed using LOCF. No other methods for dealing with missing data were considered and it is it is possible that the use of LOCF may provide a biased estimate of treatment effect since it assumes that the data is missing at random, which is not true in this case. Although LOCF was also used in the HURON[7] trial the issue is less problematic in this case because most patients were followed up for 26 weeks and treatment could not be discontinued (because the implants are not removed). Estimates of treatment effect for secondary outcomes (including VFQ-25, EQ-5D, visual acuity, VH) may be biased because data is only collected until treatment failure.

Evidence about key outcome measures could be synthesised using either absolute values at each time point or change from baseline. The use of absolute values was ruled out because of differences in response at baseline between the sham and treatment arms in HURON[7] for VFQ-25 (see

Table **14**). The sham arm has a higher mean VFQ-25 at baseline, whereas clinical advice suggests that the lower mean VFQ-25 associated with the treatment arm is likely to be more representative of the population. It was not possible account appropriately for baseline differences.

- **Treatment with adalimumab and dexamethasone is generally for different patient groups** As discussed in Section 3.3, there is only a small patient group in which it would be appropriate to compare DEX 700 and ADA, the most likely group being patients with bilateral uveitis with a temporary flare up. Consequently, an analysis that assumes that clinicians would be prepared to treat any patient in the population with any of the treatments is inappropriate.

Summary of clinical effectiveness and safety (RCTs)

Three RCTs were included in the review of clinical effectiveness; a summary of results is provided in Table 27. Two RCTs compared ADA versus placebo, for up to 80 weeks or until treatment failure, in patients with intermediate, posterior or panuveitis on high-dose oral corticosteroids: VISUAL I[4] (active uveitis) and VISUAL II[5] (inactive uveitis). Oral corticosteroids were tapered from baseline, and patients could receive up to one systemic immunosuppressant. One RCT (HURON[7]) compared DEX 700 (single 0.7mg implant) versus sham over 26 weeks' follow-up, in patients with intermediate or posterior uveitis. At baseline 25% were on systemic therapies which could be continued at a stable dose.[7] Thirteen additional studies of clinically-relevant comparator treatments (versus placebo or one another) were identified. However, due to clinical heterogeneity, differences in outcomes and lack of common comparators, it was not feasible to undertake a NMA. Therefore, the summary of clinical efficacy evidence presented here is restricted to the VISUAL I,[4] VISUAL II,[5] and HURON[7] studies.

Treatment failure in the VISUAL studies of ADA was defined as worsening of any of the following in either eye: AC cell grade, VH grade, BCVA, or new inflammatory lesion. In VISUAL I[4] (active uveitis), median time to treatment failure was 5.6 months for ADA compared to 3 months for placebo (hazard ratio (HR) 0.50 (95% CI 0.36 to 0.70, $p<0.001$). Treatment failure was experienced by 54.5% on ADA versus 78.5% on placebo. In VISUAL II[5] (inactive uveitis), median time to treatment failure was not estimable for ADA and 8.3 months for placebo; HR 0.57 (95% CI 0.39 to 0.84, $p=0.004$). Treatment failure was experienced by 39% on ADA versus 55% on placebo. In VISUAL I,[4, 50] there were significant benefits for ADA versus placebo for changes in the following (averaged across both eyes): visual acuity ($p=0.003$), inflammation (VH, $p<0.001$ and AC cell grade, $p=0.011$), macular oedema (change in central retinal thickness, $p=0.020$), VFQ-25 composite score ($p=0.010$) and EQ-5D ($p=0.044$). In VISUAL II,[5, 60] differences were not significant for ADA versus placebo for changes in any of the following (averaged across both eyes): visual acuity ($p=0.096$), inflammation (VH, $p<0.070$ and AC cell grade, $p=0.218$), macular oedema (change in central retinal thickness, $p=0.451$) VFQ-25 composite score ($p=0.160$) or EQ-5D ($p=0.836$).

In the HURON study,[7] there were significant benefits for DEX 700 versus sham for the following (measured in the study eye only): percentage of patients with VH score of zero at 8 weeks ($p<0.001$) and 26 weeks ($p=0.014$); percentage of patients with VH improvement ≥2 units at 8 weeks ($p<0.001$) and 26 weeks ($p=0.001$); percentage of patients with BCVA improvement of ≥3 lines over weeks 3 to 26 ($p<0.001$); mean BCVA improvement over weeks 3 to 26 ($p\leq0.002$); central retinal thickness at 8 weeks ($p\leq0.004$) though not at 26 weeks ($p\geq0.227$); change in VFQ-25 composite score (per patient as opposed to study eye) at 8 weeks ($p=0.007$) and 26 weeks ($p=0.001$), and; percentage of patients with ≥5-point improvement in VFQ-25 score at 8 weeks ($p<0.001$) and 26 weeks ($p<0.05$). Rescue

medications (corticosteroid injections in the study eye or new/increased systemic corticosteroids or immunosuppressants) were required in 22% in the DEX 700 arm versus 38% for sham (p=0.030).

Since ADA affects the immune system, potential risks include infections and malignancy.[3] Serious infections were higher for ADA than placebo in VISUAL I[4] (4.5% versus 1.8%) but not VISUAL II[5] (1.7% versus 1.8%). Malignancies and chronic renal failure each occurred in a total of 3 patients across both trials (ADA) versus none (placebo). Systemic AEs which were higher for ADA than placebo in at least one of the VISUAL studies[4, 5] included infections, injection site reactions, fatigue, arthralgia, myalgia, paraesthesia, hypertension and liver enzyme increases. Anti-adalimumab antibodies in patients on ADA occurred in 2.7% in VISUAL I[4] and 5% in VISUAL II.[5] There was little difference between ADA and placebo in rates of ocular AEs.

In terms of safety, risks for DEX 700 include those associated with intraocular steroids i.e. increased intraocular pressure (IOP), cataract and glaucoma as well as infection and bleeding.[6] In the HURON study,[7] raised IOP occurred in 25% (DEX 700) versus 7% (sham), while IOP ≥25 mmHg occurred in 7.1% (DEX 700) versus 1.4% (sham). Glaucoma rates were lower for DEX 700 (0%) than sham (2.7%); no patients required incisional surgery for glaucoma, while 2.6% (DEX 700 group) required laser iridotomies, and at any single time-point up to 23% in the DEX 700 group required IOP-lowering medication (not reported for sham). Cataracts in eyes that were phakic (had a natural lens) at baseline occurred in15% (DEX 700) versus 7% (sham), and cataract surgery in 1.6% (DEX 700) versus 3.6% (sham). Endophthalmitis (severe eye infection) and severe uveitis worsening occurred in 1 patient each (DEX 700) versus none for sham. Conjunctival haemorrhage occurred in 30% (DEX 700) versus 21% (sham). No systemic adverse effects (AEs) were substantially higher for DEX 700 than sham.

Table 27: Summary of clinical effectiveness

Outcome	Difference between groups: treatment effect (95% CI), p-value			
	ADA: VISUAL I (active uveitis)	**ADA: VISUAL II (inactive uveitis)**	**DEX 700: HURON At 8 weeks**	**DEX 700: HURON At 26 weeks**
Time to treatment failure (worsening of AC, VH, BCVA or new lesions)	HR=0.50 (0.36 to 0.70), p<0.001	HR=0.57 (0.39 to 0.84), p=0.004	NR	NR
BCVA (logMAR, change)	MD= -0.07 (-0.11 to -0.02), p=0.003	-0.04 (-0.08 to 0.01), p=0.096	NR	MD=NR, p=0.002
BCVA improvement ≥3 lines (15 letters)	NR	NR	MD=36.3% (24 to 49), p<0.001 RR=6.5 (2.7 to 15.8), p<0.001	MD=24.5 (11 to 38), p<0.001 RR=2.9 (1.5 to 5.5), p=0.001
BCVA improvement ≥2 lines (10 letters)	NR	NR	MD=43 (29 to 56), p<0.001 RR=3.5 (2.1 to 5.9), p<0.001	MD=30 (15 to 44) , p<0.001 RR=2.2 (1.4 to 3.4), p<0.001
VH grade (change)	MD= -0.27 (-0.43 to -0.11); p<0.001	MD= -0.13 (-0.28 to 0.01); p =0.070	NR	NR
VH grade (final)	NR	NR	MD: -0.97 (CI NR), p<0.001	MD: -0.58 (CI NR), p<0.001
% with VH = 0	NR	NR	MD: 34.9 (22 to 48), p<0.001 RR: 4.0 (2.0 to 7.6), p<0.001	MD: 16.7 (4 to 30), p=0.014 RR: 2.2 (1.1 to 4.1), p=0.02
% with VH improvement ≥2	NR	NR	MD=NR, p<0.001	MD=NR, p=0.001
AC cell grade (change)	MD= -0.29 (-0.51 to -0.07), p=0.011	MD= -0.14 (-0.37 to 0.08), p=0.218	NR	NR
Macular oedema (change in macular thickness, μm)	NR	NR	MD= -87.0 (-147 to -27), p=0.004	MD= -14.7 (-66 to 37), p=0.58
Macular oedema (change in macular thickness, % change)	MD= -11.4 (-20.9 to -1.8); p= 0.020)	MD= -2.3 (-8.5 to 3.8); p=0.451	NR	NR
VFQ-25 composite score (change)	MD=4.20 (1.02, 7.38), p=0.010	MD=2·12 (–0·84, 5·08), p=0.160	MD=NR, p=0.007	MD=NR, p=0.001
% with ≥5-point improvement in VFQ-25	NR	NR	MD=NR, p<0.001	MD=NR, p<0.05
EQ-5D (change)	MD=0.04 (0.00 to 0.07), p=0.044	MD=0.00 (-0.03 to 0.04), p =0.836	NR	NR
% requiring rescue medications	NR	NR	NR	MD=NR, p=0.030
AC, anterior chamber; BCVA, best-corrected visual acuity; CI, confidence interval; HR, hazard ratio; logMAR, logarithm of the Minimum Angle of Resolution; MD, mean difference; NR, not reported; RR, relative risk; VFQ-25, Visual Functioning Questionnaire-25; VH, vitreous haze.				

6. ASSESSMENT OF COST-EFFECTIVENESS

Section 6.1 presents a systematic review of existing cost-effectiveness evidence for treatments given to mainly adult patients with non-infectious uveitis. Section 6.2 provides a description of a *de novo* model developed by the AG to assess the cost-effectiveness of dexamethasone in patients with active uveitis, adalimumab in patients with active uveitis and adalimumab in patients with inactive uveitis, all compared with current practice. The results and a discussion of this analysis are also presented in Section 6.2.

6.1 Systematic review of existing cost-effectiveness evidence

6.1.1 Methods

A comprehensive search was undertaken to systematically identify economic evaluations and quality of life studies for patients with active non-infectious intermediate uveitis, posterior uveitis and/or panuveitis.

The following electronic databases and clinical trials registries were searched from inception for economic evaluations:

- MEDLINE: Ovid, 1946 to Present
- MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations: Ovid, 1946 to Present
- EMBASE: Ovid, 1980 to present
- The Cochrane Library: Wiley Interscience
- Health Technology Assessment Database (HTA), 1995 to present
- NHS Economic Evaluation Database (NHS EED), 1995 to 2015
- Cumulative Index to Nursing and Allied Health Literature (CINAHL): EBSCO, 1982 to present
- Web of Science Citation Index: Thomson Reuters, 1899 to present
- Conference Proceedings Citation Index (CPCI): Thomson Reuters, 1990 to present

The search strategy was comprised of Medical Subject Headings (MeSH) or Emtree Thesauri terms and free-text synonyms for 'uveitis'. Searches were translated across databases and were neither limited by language nor publication date. The search strategies are presented in Appendix 1. Search filters designed to identify economic evaluations and quality of life studies were used on MEDLINE and other databases where appropriate. Reference and citation searching of included papers was undertaken.

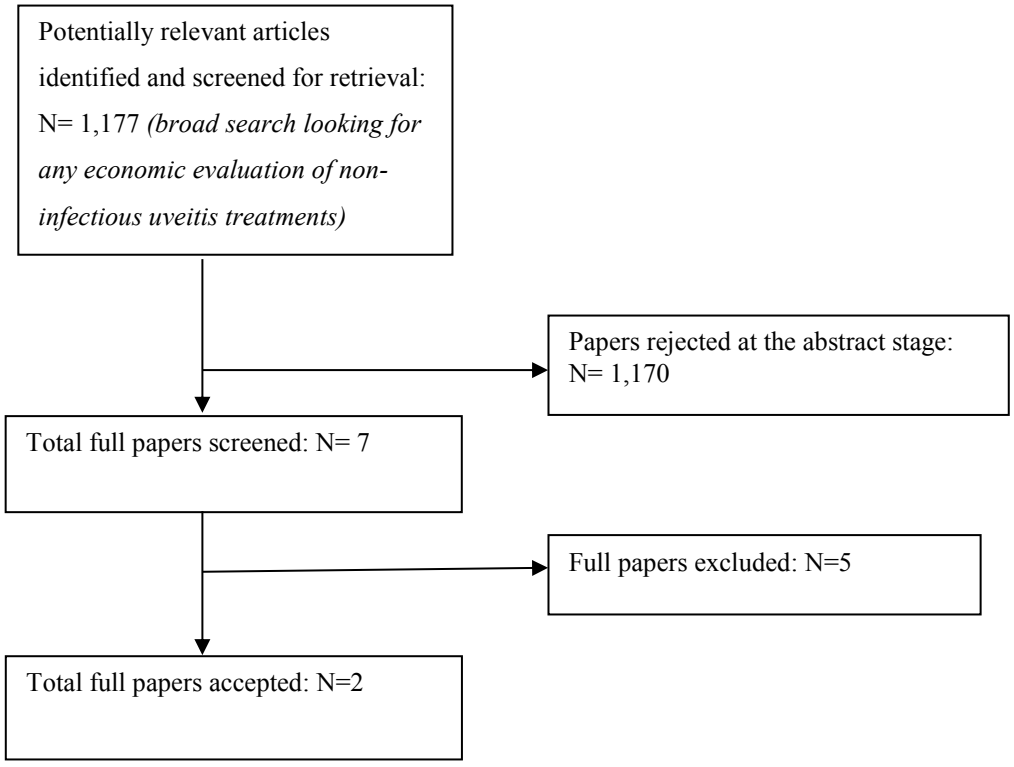
The inclusion criterion was economic evaluations of treatments given to mainly adult patients for non-infectious uveitis. This took a deliberately broad perspective and was not limited to treatment with adalimumab or dexamethasone. Studies which reported only costs were excluded, although these were

marked as potentially useful for informing the model parameters. Study selection was undertaken by one reviewer (IB) and checked by a second reviewer (HS). Critical appraisal of included studies was undertaken using a combination of key components of the British Medical Journal checklist for economic evaluations together with the Eddy checklist on mathematical models (see Appendix 7).[86, 87]

6.1.2 Results

The electronic literature searches identified 1,177 potentially relevant economic analyses of treatment for non-infectious uveitis. Of these, only seven studies appeared to relate to the economic evaluation of non-infectious uveitis and full texts of these papers were obtained for review. Two of these studies met the inclusion criteria; one of these included studies was published only as a conference abstract. The number of studies screened and included within the review is shown in Figure 10.

Figure 10: Summary of economic evaluation selection and exclusion



Justification of excluded studies at the full paper screening stage

The review by the Health Technology Inquiry Service[88] was excluded following full paper screening as it did not identify any cost-effectiveness studies. The study reported by Ang et al.[89] was excluded because it related to an analysis of interventions for tuberculous uveitis rather than non-infectious uveitis and compared diagnostic testing strategies rather than treatments for diagnosed disease. Ramanan et al.[90] and Ramanan et al.[91] were excluded because they were limited to children and because

they did not include an economic analysis. The study reported by Nguyen et al.[92] was excluded because it was not an economic evaluation.

Included economic evaluations

The key characteristics of the two studies identified for inclusion within the review are shown in Table 28 and are discussed briefly below. Neither of these studies included adalimumab or dexamethasone as interventions or comparators. One of the economic analyses was based on a semi-Markov model, whilst the other extrapolated cost and HRQoL data collected during the MUST trial.[74, 93] The two economic evaluations compared a different set of treatments.

Table 28: Characteristics of studies included in the cost-effectiveness review

Author	**Padula *et al.*** [94]	**Sugar *et al.*** [95]
Country & year of publication	USA, 2011	USA, 2014
Type of economic analysis	Cost-utility analysis	Cost-utility analysis
Health economic perspective	Societal	Payer's perspective for costs and the patient's perspective for outcomes.
Health economic comparisons (listed interventions)	Infliximab Systemic steroids Methotrexate	Fluocinolone acetonide intraocular implant Oral corticosteroid with immunosuppressive agents as needed
Population characteristics	Patients with sarcoid posterior uveitis.	Patients aged 13 years or older with non-infectious intermediate, posterior, or panuveitis in one or both eyes (active within <= 60 days) for which systemic corticosteroids were indicated (excluding those requiring systemic therapy for non-ocular indications)
Time horizon	Lifetime	3 years
Health economic outcomes	Incremental cost per QALY gained	Incremental cost per QALY gained
Modelling approach	Semi-Markov model	Extrapolation of trial data

Padula et al. A cost-effectiveness analysis of off-label biologics to treat sarcoid posterior uveitis versus standard of care: Comparing infliximab to methotrexate and systemic steroids[94]

The study by Padula et al[94] was reported only as a conference abstract. Padula et al.[94] present the methods and results of a cost-effectiveness analysis of infliximab versus methotrexate and versus systemic steroids over a lifetime horizon. The economic evaluation uses a semi-Markov approach to estimate health outcomes and costs. Patients enter the model following the onset of sarcoid posterior uveitis. No further information was provided about the population reflected in the model. Cost-effectiveness is evaluated in terms of the incremental cost per QALY gained from a societal perspective.

Probabilities, health utilities, and costs used in the model were reported to be taken from the literature, although parameter values were not reported in the abstract. It was not specified whether a systematic review was conducted. Costs and health outcomes were discounted at a rate of 3% per annum. Costs were expressed in 2010 US dollars ($). The authors conducted univariate sensitivity analyses, threshold analyses, and probabilistic sensitivity analysis (PSA) using 10,000 simulations.

The ICER for methotrexate compared with systemic steroids was estimated to be $10,053 per QALY gained. Methotrexate dominated infliximab in the base case. However, if a patient's health utility after successful recovery was below 0.750 (base case value of 0.84), then infliximab produced greater net benefit than methotrexate assuming a willingness-to-pay (WTP) threshold of $50,000 per QALY gained. The PSA suggested that the probability of methotrexate dominating infliximab was 0.60.

It is not possible to assess the validity of the model since only limited information is provided within the conference abstract. The AG notes that this analysis does not include either of the interventions being assessed within this appraisal (dexamethasone and adalimumab) and the model does not appear to differentiate between unilateral and bilateral uveitis, which may be associated with different cost-effectiveness results. There is insufficient information provided within the abstract for this analysis to be useful in the current appraisal.

Sugar *et al.* Cost-effectiveness of fluocinolone acetonide implant versus systemic therapy for noninfectious intermediate, posterior, and panuveitis[95]

Sugar *et al.*[95] present a cost-effectiveness analysis of fluocinolone acetonide intraocular implant compared with oral corticosteroid with immunosuppressive agents. Costs and health benefits were estimated from data collected during the MUST trial.[74] The economic analysis used a time horizon of three years and costs and benefits were discounted at a rate of 3% per annum. The authors used a payer's perspective for costs and the patient's perspective for outcomes. The authors estimated the cost to a payer to maximise health benefits by using the more effective, but more expensive, treatment.

The within-trial data (differences in cost and utility), reported at two years follow-up, were extrapolated by a further year for a three year time horizon. The difference in the mean total cost of treatments was

determined with a linear regression with a saturated means model. The history of the disease was modelled through a sequence of utility values measured during the trial at different points in time. No health states were used. Uncertainty was assessed using bootstrapping and was represented using cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs).

For bilateral uveitis, the fluocinolone acetonide implant for both eyes was estimated to generate 0.057 additional QALYs at an additional cost of $16,900; the ICER was reported to be $297,800 per QALY gained. The probabilities of the fluocinolone acetonide implant being cost-effective compared with systemic therapy at willingness to pay (WTP) thresholds of $50,000 and $100,000 per QALY gained was 0.003 and 0.04, respectively. For unilateral uveitis, the implant resulted in 0.130 additional QALYs at an additional cost of $5300; the ICER was reported to be $41,200 per QALY. The probabilities of the implant being cost-effective compared with systemic therapy at WTP thresholds of $50,000 and $100,000 per QALY gained were 0.53 and 0.74, respectively.

The study highlights the importance of considering unilateral and bilateral uveitis separately within future economic evaluations, in terms of: (i) the cost difference between types of treatments; (ii) quality of life impacts, and; (iii) the greater risk to vision of an operative procedure on both eyes compared with one eye. However, this study does not consider the cost-effectiveness of the implant in one eye for patients with bilateral uveitis since all patients with bilateral uveitis within the MUST trial were given an implant in both eyes.[74] The model has several additional key limitations:

- All relevant comparators were not included in the model. Systemic steroids and immunosuppressants are assumed to be the gold standard, as they are the only included comparator of the fluocinolone acetonide implant; however, there is no discussion about whether this is appropriate.
- Adverse events were not taken into consideration.
- It is not clear how the two years of data from the MUST trial were extrapolated to the three-year time horizon.
- It is not clear whether the implant would have benefits after this three-year period.
- No model validation was reported.
- The analysis of uncertainty is not well described.

Company submissions

Neither AbbVie[55] (adalimumab) nor Allergan[47] (dexamethasone) submitted a health economic model. Within their submission, AbbVie provide no discussion of cost-effectiveness, and present a budget impact estimate based on the acquisition costs of adalimumab only.

Within their submission, Allergan argue that dexamethasone has been recommended by NICE for the treatment of macular oedema secondary to retinal vein occlusion[96] and that the costs per patient associated with dexamethasone are comparable, the incremental gains in visual acuity are greater in posterior segment uveitis based upon the trial data from the individual trials. This argument fails to consider the incremental (rather than absolute) cost of dexamethasone treatment compared with current treatment. Allergan also submitted a budget impact model, which takes into account the costs of treatment and monitoring, but not of treating events associated with uveitis or adverse events associated with treatment (see Section 7).

Summary of review of existing cost-effectiveness studies

No existing studies have assessed the cost-effectiveness of either dexamethasone or adalimumab within this patient population. Only one published health economic model of non-infectious uveitis exists. This study was subject to several limitations, including: poor reporting of some of the methods, validation and uncertainty analysis; not taking into account adverse events, and; the use of a three-year time horizon, which may not fully capture all impacts of the treatments.

6.2 Independent economic assessment

6.2.1 Methods

This section provides details of a Markov model developed by the AG which is used to evaluate the cost-effectiveness of adalimumab and dexamethasone within their licensed indications for non-infectious posterior segment-involving uveitis compared with current practice, from a NHS and PSS perspective. A cohort of patients with a mean age of 44.8 is followed over a lifetime. All costs and QALYs are discounted at a rate of 3.5% per year. Adalimumab and dexamethasone are not compared against each other. This is as a consequence of their different use in clinical practice (see Section 3.3) and, because in the limited indications where there could be a choice for the clinician regarding which treatment to use, there is a lack of evidence as detailed in Section 5.2.3.

Table 29 describes key features of the model for both adalimumab and dexamethasone.

Table 29: Model summary (base case analysis)

	Adalimumab	**Dexamethasone**
Population	People with non-infectious intermediate, posterior or pan uveitis with (a) active disease (VISUAL I[4] and (b) inactive disease (VISUAL II[5])	People with non-infectious intermediate, posterior or pan uveitis with active disease (HURON[7])
Intervention	(a) Adalimumab until treatment failure + LCP(VI) (b) Adalimumab until treatment failure + LCP(VII)	One dexamethasone implant + LCP(H)
Comparator	(c) LCP(VI) (d) LCP(VII)	LCP(H)
Outcome used from trial	EQ-5D	VFQ-25
Time horizon	Lifetime	
Discounting	3.5% per year for costs and QALYs	
Treatment discontinuation	Parametric survival curve of time to treatment failure fitted to VISUAL I and II trial data	Patients are only given one dexamethasone implant
Method for estimating QALYs (during trial period)	Using directly measured EQ-5D at each time point until treatment failure, when patients revert to baseline utility, adjusted for age.	Using VFQ-25 data captured at each time point in the trial mapped onto EQ-5D.
Method for estimating QALYs (following trial period)	Patients who have not failed treatment retain the averaged utility from month 12 – 18 of the trial (due to small patient numbers), adjusted for age. Patients who fail treatment revert to baseline utility, adjusted for age.	Assumes utility remains the same for four weeks following the trial and then returns to baseline by week 30, adjusted for age.
Adverse events (except blindness)	Cataract, raised IOP, glaucoma, serious infections, hypertension, fractures, diabetes. Impact on HRQoL associated with these AEs assumed to be captured within the VFQ-25/ EQ-5D.	
Permanent blindness (comparator)	No blindness prior to treatment failure. Constant rate of blindness after treatment failure based on Dick *et al.*[24]	Constant rate of blindness based on Dick *et al.*[24]
Permanent blindness (intervention)	No blindness prior to treatment failure. Constant rate of blindness after treatment failure based on Dick *et al.*[24]	Relative risk for blindness of 0.5 for 30 weeks following implantation
Treatment following remission	For all patients, treatment will continue until treatment failure	For all patients, treatment will continue until treatment failure

	Adalimumab	Dexamethasone
LCP(H): Limited current practice based on HURON; LCP(VI): Limited current practice based on VISUAL I; LCP(VII): Limited current practice based on VISUAL II		

Due to the substantial uncertainties associated with the above assumptions due to the limited evidence base, most of these are altered within exploratory analyses to test their impact upon the model results.

6.2.1.1 Model description

Patient population

The model population consists of people with non-infectious intermediate, posterior or pan uveitis. Patients receiving dexamethasone are assumed to have active disease, whilst the model assessed the cost-effectiveness of adalimumab separately for patients with active and inactive disease. An analysis was undertaken to explore the cost-effectiveness of dexamethasone use in one eye in patients with unilateral disease and bilateral disease as separate subgroups; the trial did not provide data separately for these groups and hence it is considered to be exploratory. Owing to the lack of evidence, it was not possible to explore additional subgroups. A cohort of uveitis patients are assumed to enter the model with a mean age of 44.8, based on the mean ages within HURON[4,5,7] and are followed over a lifetime. The model population is limited to adults aged 18 years and over because the marketing authorisations for the technologies being considered relate only to this group.

Interventions

The two technologies considered were adalimumab (40mg every two weeks until treatment failure) and the dexamethasone implant (0.7mg, once only in the base case).

Within the clinical trials of adalimumab (VISUAL I[4] and II[5]), patients were already receiving high-dose corticosteroids at randomisation, plus a corticosteroid burst was given to all patients at the start of the VISUAL I trial; corticosteroids were tapered to zero by week 15 (VISUAL I) or week 19 (VISUAL II). Clinical advisors to the AG suggest that this is also likely to reflect clinical practice, although the SmPC suggests that adalimumab may be given alongside corticosteroids or alone.[3] Given the evidence available, for patients with active disease, the model considers the cost-effectiveness of adalimumab plus an initial oral corticosteroid burst, rather than adalimumab alone.

The dexamethasone implant can be administered in the affected eye to unilateral patients, in one eye for patients with bilateral disease, or in both eyes at staggered intervals for patients with bilateral disease. Patients could also receive more than one consecutive implant. Clinical advisors to the AG suggest that dexamethasone would most likely be used when disease affects only one eye (or is more severe in one eye in the case of asymmetric disease), or to treat a temporary flare-up in one or both

eyes, where systemic disease is not present or is well-controlled. The base case model assumes that patients would receive one dexamethasone implant in one affected eye, as within the HURON trial.[7] There are no RCTs which assess the use of more than one consecutive implant or the use of implants in two affected eyes. However, there are several non-randomised trials with 12–24 months follow up, which allow repeat implants.[22, 48, 49] These studies consistently report that after around six months, patients' outcomes return to those at baseline; and that up to three repeat implants are each likely to have a similar treatment effect. Given the limited evidence around repeat implants, this is explored within sensitivity analysis. Implants in both eyes have also been assessed in one study, in which 3/11 (27%) patients receiving implants in both eyes had a response (reduced CRT and improved BVCA) in the second eye.[22] Clinical advisors to the AG suggest that it is more likely that systemic treatment would be used if both eyes required treatment; however, the direction of the ICER for treatment in both eyes compared with one eye is considered in the discussion section of this report (see Section 8).

Comparators

The two technologies were compared independently with current practice, which includes a range of immunosuppressants (such as methotrexate, mycophenolate mofetil, cyclosporine and azathioprine) and corticosteroids. Given the concerns regarding the robustness of undertaking an NMA (see Section 5.3.3), within the base case analysis, current practice is assumed to be equivalent to the control arm (sham or placebo) of the clinical trials of the interventions. In the VISUAL trials of adalimumab,[4, 5] patients received initial corticosteroids which were tapered by 15 weeks (VISUAL I) and 19 weeks (VISUAL II), and 32% (VISUAL I) and 48% (VISUAL II) of patients were receiving one immunosuppressant at baseline (across arms), which they were able to maintain according to the study protocol. Given that a greater proportion of patients in practice are likely to receive systemic corticosteroids, these comparators are denoted throughout as limited current practice, based on VISUAL I or II (LCP(VI), LCP(II)). In the HURON trial of dexamethasone,[7] patients were allowed rescue therapy with corticosteroids or immunosuppressants and 25% were using systemic immunosuppressants or anti-inflammatory treatment at baseline, which they were able to maintain according to the study protocol. This comparator is denoted throughout as limited current practice based on HURON (LCP(H)). Apart from rescue therapy with immunosuppressants within the HURON study, these proportions were similar across arms of HURON and VISUAL I and II.[4, 5, 7] In current practice, a greater proportion of patients would receive systemic immunosuppressants or anti-inflammatory treatment than in the control arms of the pivotal studies; consequently, the base case analysis is likely to underestimate both the effectiveness and the adverse event profile of current practice, as well as the costs associated with treatment. Within exploratory analyses, the AG assessed the impact on the results of increasing the value of these parameters within the model. However, it should also be noted that in clinical practice a greater proportion of patients being treated with adalimumab and dexamethasone are also likely to receive concomitant treatment.

Outcomes

The model estimates the incremental cost per QALY gained for each intervention compared with current practice.

The VISUAL trials[4, 5] and the HURON trial[7] each report VFQ-25 health-related quality of life (HRQoL) data at baseline and at each follow-up visit. The VISUAL trials also report EQ-5D data at baseline and at each follow-up visit. The model uses the EQ-5D data directly for modelling the effectiveness of adalimumab. The HURON trial reported EQ-5D data at baseline but not at subsequent time points.[7] It was therefore not possible to use the EQ-5D data directly; however, Allergan shared patient-level data from the HURON trial with the AG which allowed an analysis of the relationship between VFQ-25 and EQ-5D using the baseline data (see Section 6.2.1.2). It is necessary to convert VFQ-25 data to EQ-5D utilities in order to estimate QALYs for each technology[97]

The use of the outcomes from the HURON trial[7] representing vision and inflammation (visual acuity, VH) were considered by the AG as an alternative to the use of VFQ-25 for estimating QALYs; however, the VFQ-25 outcome was preferred because of the difficulties associated with using vision as an outcome in uveitis and capturing all impacts of the interventions (see Section 3.1). Clinical advisors to the AG suggested that clinicians measure ocular outcomes based upon multiple factors, including visual acuity, VH and macular oedema. The VFQ-25 captures multiple components to vision, as well as broader considerations such as general health and the vision-related impact on ability to drive and undertake normal activities. It is also essential to capture the adverse events associated with the treatments and it is difficult to determine the utility decrements associated with the multiple interacting adverse events associated with these treatments. The AG considers that the VFQ-25 should largely capture the impact of adverse events, as well as treatment effects, upon HRQoL.

The presence of unilateral or bilateral uveitis is important in terms of estimating outcomes for several reasons. The BCVA in the better-seeing eye is more representative of quality of life than the BCVA in the worst-seeing eye.[98] In addition, a patient with bilateral disease is expected to have a lower quality of life on average than a patient with unilateral disease. Thus, a person with bilateral disease has more scope to benefit from treatment. However, in patients with bilateral disease receiving local treatment, the choice of study eye is important in determining the extent to which quality of life can increase.

In the VISUAL I and VISUAL II trials, 91% and 96% of patients had bilateral disease, respectively.[4, 5] [56, 5756, 5756, 5756, 57]Clinical advice received by the AG suggests that this is representative of patients who would be given adalimumab in practice because it is a systemic treatment. Within the HURON trial,[7] whether patients had unilateral or bilateral disease was not recorded. Based upon the patient level data provided by Allergan, the proportion of patients with VH that was greater than zero in the non-study eye was 51%; clinical advisors to the AG stated that this suggests that at least 51% of patients had

bilateral disease. Within the HURON trial, where patients had bilateral uveitis, the right eye was chosen for treatment.[7] This resulted in the better-seeing eye being treated in 10.7% and 17.1% of cases for DEX 700 and sham respectively.

Given that the presence of unilateral or bilateral uveitis is not reported in HURON,[7] it is not possible for the AG to undertake robust subgroup analysis around this factor. The base case model is therefore dependent on the assumption that the patients included within the HURON trial and the way in which dexamethasone is used within the trial would be representative of its use in practice. It is not possible to make robust conclusions about the subgroups separately in terms of cost-effectiveness; however an exploratory subgroup analysis has been undertaken (see Section 6.2.1.4). As described within Section 3.1, it is expected that around 70-80% of this patient population would have bilateral disease. However, it may be that because dexamethasone is a local treatment, patients with unilateral disease are more likely to be selected for dexamethasone both within the trial and in practice. Given that patients with bilateral disease have a greater capacity to benefit from treatment due to the BCVA of the better-seeing eye being the best predictor of quality of life, and treatment in one eye would cost the same whether given to a person with unilateral or bilateral disease, if the trial has a lower proportion of bilateral cases than in practice, then the effectiveness of dexamethasone may be underestimated. Conversely, if the trial has a higher proportion of bilateral cases than in practice, then the effectiveness of dexamethasone may be overestimated.

Time horizon

The time horizon of the model is the lifetime of patients (up to age 100 years) and a starting age of 44 years was used, representing the average age of patients with non-infectious posterior segment-involving uveitis across the HURON and VISUAL trials.[4, 5, 7] A time cycle of two weeks was chosen owing to this being the time between administration of adalimumab doses and when patients would also be assessed for disease progression. This is also a sufficiently short time cycle to capture all relevant clinical events associated with dexamethasone and current practice.

Discounting

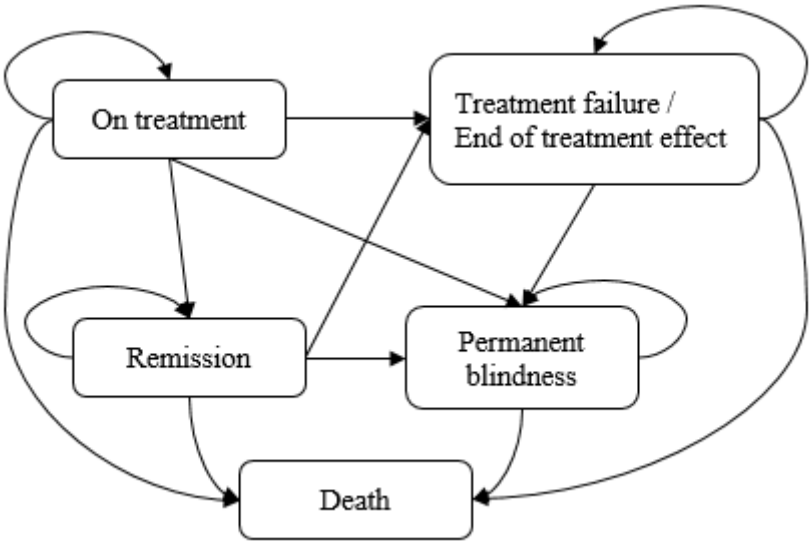
All costs and QALYs are discounted at a rate of 3.5% per year.

6.2.1.2 Model structure

The structure of the AG model is presented in Figure 11. The model includes five health states: (i) treatment: no permanent blindness; (ii) treatment failure: no permanent blindness; (iii) permanent blindness; (iv) remission (no treatment); and (v) death. For dexamethasone, treatment is one implant which is assumed to be effective for six months, at which time patients will move to the treatment failure health state if they have remained in the treatment state until this time. Patients in the LCP(H) group

begin in the 'treatment failure' state. Patients may discontinue adalimumab due to treatment failure, defined by the VISUAL trial criteria,[4, 5] at which time they will move to the second health stat e if they have remained in the treatment state until this time. Patients in the LCP(VI) and LLCP(VII) groups also begin in the treatment state and move to 'treatment failure' once they have met this criteria. Within the treatment state, HRQoL (defined by VFQ-25 or EQ-5D) could be improved due to the treatment effect or due to a reduction in adverse events. Treatment may also reduce the risk of experiencing permanent damage to the eye, resulting in a decreased risk of permanent legal blindness. Once a patient experiences legal blindness in the model, they can either remain in this health state or progress to death. Patients may also enter remission, whereby they do not receive further treatment, but they maintain the benefit of the previous treatment. Within the base case, the proportion of patients experiencing remission is assumed to be zero; however, the impact of increasing this proportion is considered within the exploratory analyses. An analysis was undertaken to explore the cost-effectiveness of dexamethasone use in one eye in patients with unilateral disease and bilateral disease as separate subgroups; the trial did not provide data separately for these groups and hence it is considered to be exploratory. Owing to the lack of evidence, it was not possible to explore additional subgroups.

Figure 11: State transition diagram of the decision model



6.2.1.3 Estimation of model parameters

Treatment discontinuation

In the base case analysis, the dexamethasone implant is assumed to be administered only once to one eye and the efficacy is assumed to last for 30 weeks, based on the HURON trial data.[7]

Patients may discontinue adalimumab as a consequence of the four criteria for treatment failure used within the VISUAL trials, including: (i) development of new inflammatory lesions; (ii) worsening of AC cell grade; (iii) worsening of VH grade, or; (iv) worsening of visual acuity.[4, 5] Treatment discontinuation was modelled using parametric curves fitted to Kaplan-Meier curves for time to treatment failure from the trials. The Kaplan-Meier curves for time to treatment failure included in the VISUAL I and II CSRs[50, 60] were digitised and IPD reconstructed using the methods described by Guyot *et al.*[99] A number of parametric curves were fitted to the data using the flexsurvreg R package. Table 30 and Table 31 present the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) scores for statistical goodness-of-fit.

Table 30: AIC and BIC scores for parametric curves fitted to the KM for time to treatment failure in the adalimumab arm in the VISUAL I trial

	Arm	Log normal	Gamma	Weibull	Gompertz	Exponential	Log logistic
AIC	ADA	374.7	388.5	384.7	370.3	403.4	377.5
	Placebo	435.9	465.7	456.5	438.4	486.7	438.9
BIC	ADA	377.4	391.2	387.4	373.0	407.1	380.2
	Placebo	438.5	468.4	459.2	441.1	490.3	441.5

Table 31: AIC and BIC scores for parametric curves fitted to the KM for time to treatment failure in the adalimumab arm in the VISUAL II trial

	Arm	Log normal	Gamma	Weibull	Gompertz	Exponential	Log logistic
AIC	ADA	370.6	378.9	377.3	364.9	382.2	373.1
	Placebo	403.5	408.4	406.1	403.7	428.5	403.2
BIC	ADA	373.3	381.6	380.0	367.7	385.9	375.8
	Placebo	406.2	411.2	408.8	406.4	432.3	406.0

It should be noted that these are relative measures of goodness-of-fit and it is possible that other models not tested here could provide a better fit to the data. Figure 12, Figure 13, Figure 14 and Figure 15 show the Kaplan-Meier data and the fitted parametric distributions for VISUAL I and II for the adalimumab and comparator groups.

Figure 12: Observed and fitted curves for time to treatment discontinuation in the adalimumab arm in VISUAL I

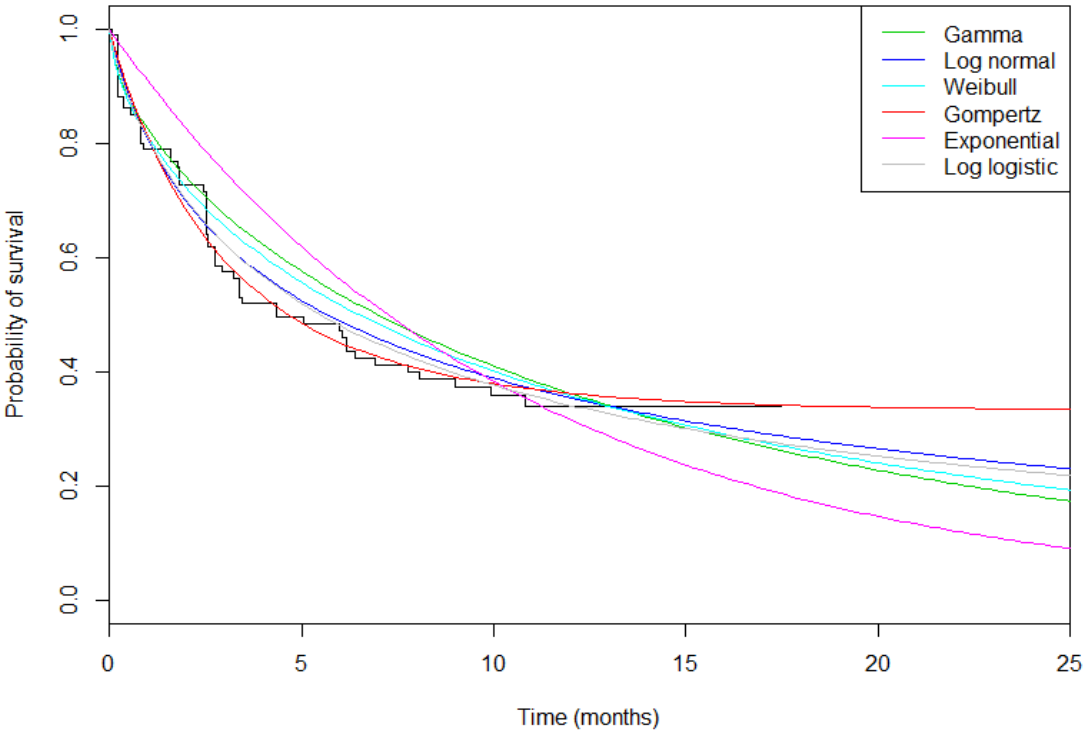


Figure 13: Observed and fitted curves for time to treatment discontinuation in the placebo arm in VISUAL I

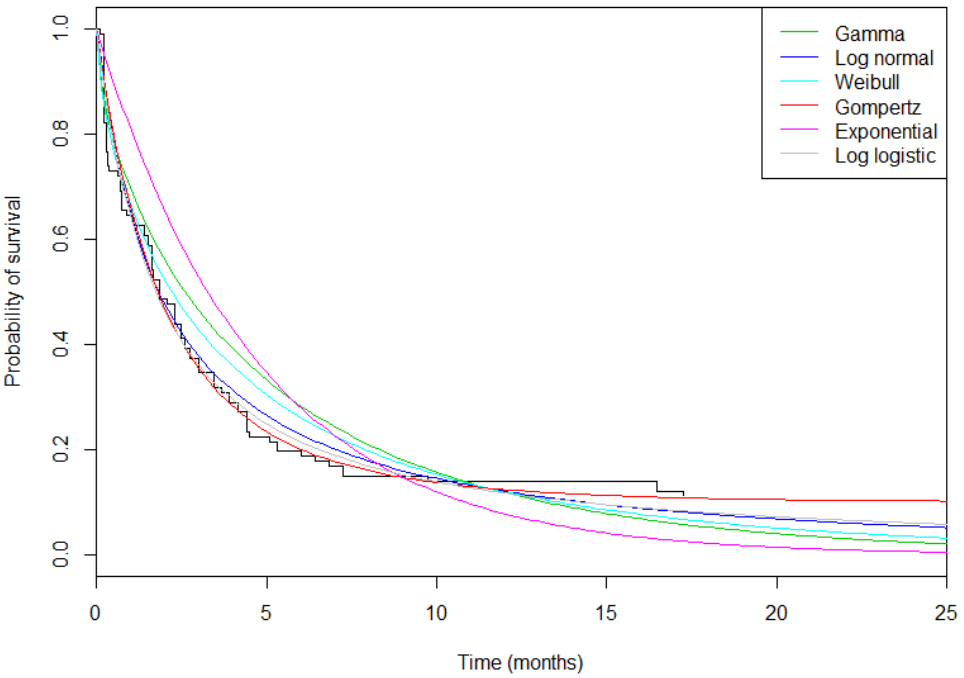


Figure 14: Observed and fitted curves for time to treatment discontinuation in the adalimumab arm in VISUAL II

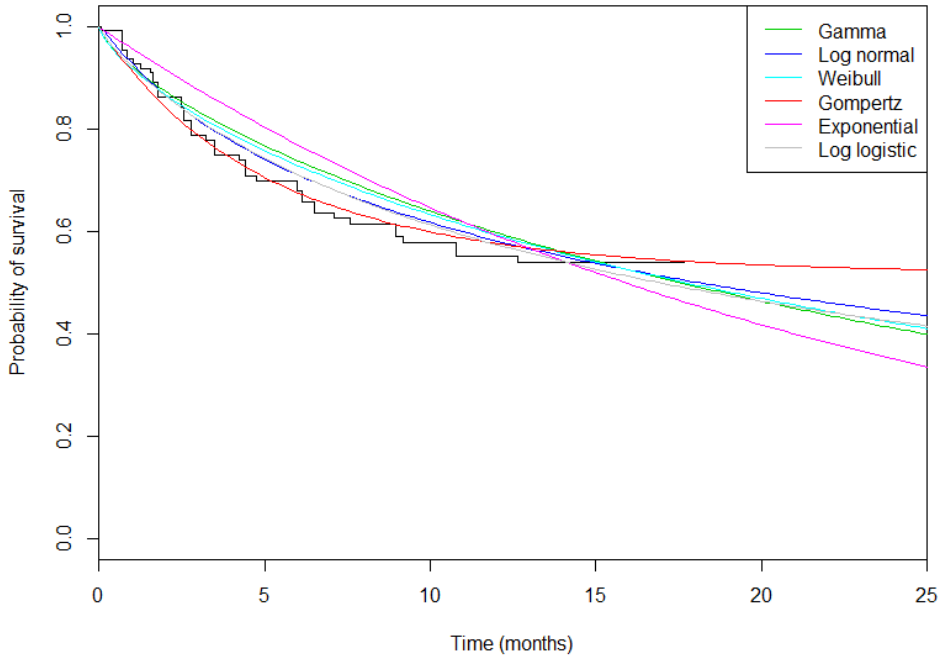
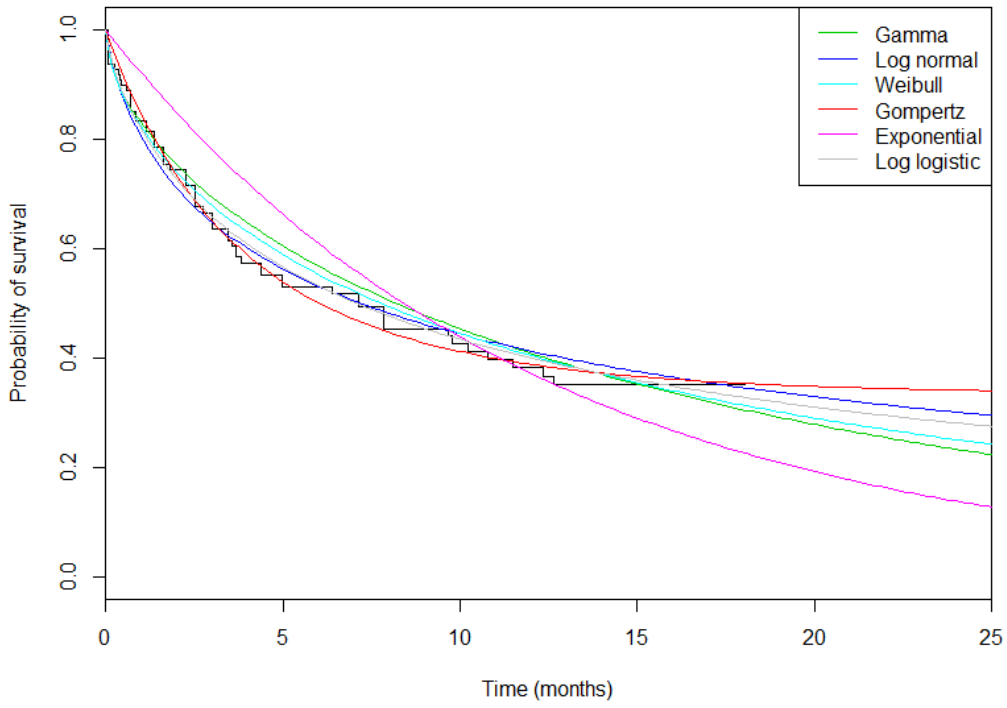


Figure 15: Observed and fitted curves for time to treatment discontinuation in the placebo arm in VISUAL II



The statistical analysis suggested that, of those tested, the parametric distributions with the best fit to the data are the Gompertz and the log normal distributions for both the adalimumab group and the placebo group in VISUAL I and II. Clinical advisors to the AG suggested that it is clinically plausible that some patients would remain on adalimumab for years; hence the plateauing of these curves seems potentially reasonable. However, the Gompertz curve seems clinically implausible since observational studies of adalimumab in similar patient populations, have suggested that patients are likely to continue to fail treatment in the longer term.[100, 101] The log normal distribution appears to be the most plausible for the placebo arm so that patients do fail on treatment relatively quickly. The log normal distribution also appears clinically reasonable for the adalimumab group. It should be noted that although based on these predictions alone some patients would continue to receive treatment for an implausibly long period of time, within the model patients may die of other causes which negates the need for a cure model to be employed.

It was assumed that after patients fail and discontinue treatment with adalimumab, or six months after the dexamethasone implant is injected, they stay on a limited current practice which includes a range of immunosuppressants (such as methotrexate, mycophenolate mofetil, cyclosporine and azathioprine) and corticosteroids for a proportion of patients. It was also assumed that the treatments are only effective whilst they are being given. Therefore, patients who are no longer being treated with adalimumab, and patients who received the dexamethasone implant more than six months ago, will accrue no additional health gains.

Permanent legal blindness

The VISUAL and HURON trials did not report any occurrence of permanent legal blindness, which is likely to be due to the short duration of the clinical trials.[4, 5, 7] However, it may be that the use of adalimumab or dexamethasone could prevent damage to the eye, which may in turn prevent future blindness. Conversely, it is possible that the adverse events associated with treatment (such as raised IOP) could lead to an increased risk of blindness via glaucoma. We define blindness as a BCVA of 20/200 or less in the better-seeing eye, according to the UK definition of legal blindness.[102] The AG considered two approaches for modelling permanent blindness based on the evidence from the key RCTs. The first was to extrapolate the decrease in BCVA over time using the mean change and distribution from the trials and to estimate the proportion of patients who would go below the legal blindness threshold in each group. The AG considered that this approach had three weaknesses: (i) the follow-up period of the clinical trials was not long enough to capture the total impact on visual acuity because damage to the eye does not always immediately impact visual acuity; (ii) there are different trajectories according to the cause of the damage to the eye which could not be appropriately captured by a single parametric distribution; and (iii) for patients with unilateral disease, additional assumptions about the probability of blindness in both eyes would need to be made.

The second approach considered by the AG was to use outcomes from the trials such as glaucoma and macular oedema as surrogate outcomes for blindness in the future. In principle, this would allow a more accurate estimate of blindness over time, and could exclude outcomes such as cataract for which blindness is reversible via surgery. However, the AG did not identify any evidence that could provide a link between these shorter-term outcomes to blindness. The only evidence of blindness caused by uveitis identified by the AG was cross-sectional and did not specify time to blindness.[22, 32] This means that populating the model would require elicitation or an assumed distribution for how long it would take patients to become blind, and to extend this beyond the period of the cross-sectional study data. In addition, the key long-term outcome to include in the model is blindness in both eyes given that the BCVA in the better eye is the best predictor of quality of life and blindness in both eyes would incur the greatest costs. The cross-sectional studies do not provide sufficient information in order to estimate the probability of blindness in both eyes; hence numerous assumptions would be required. The identified studies also include patients with anterior uveitis. The AG requested the patient-level data from one of the cross-sectional studies[22] in order to be able to predict blindness over time from the outcomes reported within the clinical trials. However, these data were not provided. Given the number of assumptions that would be required to undertake this analysis in the absence of patient-level data, and the low proportions of patients reported to have glaucoma (<3% in any arm) and new cases of macular oedema (<8% in any arm) in the clinical trials,[4, 5, 7] the AG decided that adopting such a complex analysis within the model may produce potentially misleading results.

Therefore, a simpler approach was taken, and the assumptions were tested within exploratory analyses. For the base case analysis, clinical experts to the AG helped to identify sources which could be used to estimate a constant blindness rate associated with (limited) current practice. All studies identified were cross-sectional rather than longitudinal. The best source of evidence was considered to be a study by Dick *et al.*[24] because all patients (n=1769) had posterior segment, non-infectious uveitis. The study used a retrospective analysis of insurance claims data. A constant rate of blindness and uncertainty around this parameter was estimated by the AG based upon the proportion of patients going blind within the study by Dick *et al*.[24] and the mean follow-up time. By 10 years, this study predicted that 6.6% of patients would go legally blind, in the absence of death from other causes. The proportion of patients who had unilateral and bilateral disease is not reported within the study. Two alternative similar sources were also identified as being potentially relevant: Tomkins-Netzer *et al.*[25] and Durrani *et al.*[16] The rate derived from Tomkins-Netzer *et al.* was deemed to be an underestimate by one of the clinicians consulted by the AG (personal communication with Alastair Denniston) and included a wider population than the target population of the current appraisal (including patients with infectious and anterior uveitis). The rate derived from Durrani *et al.* was substantially higher than the rate derived from Dick *et al.*[24] but it also included a wider population and as the authors warned, “being a tertiary referral centre, more patients are likely to suffer from severe, often bilateral uveitis" and the authors

acknowledged that the results of their study "could not be applied to the general population because of the tertiary nature of the patient population". The AG explored the impact of using blindness rates based on these other two sources in exploratory analyses (see Sections 6.2.1.4 and 6.2.2).

As discussed above, there is no evidence around the treatment effect for adalimumab or dexamethasone on legal blindness. In order to model the impact of treatment with adalimumab upon the rate of blindness, given the strict criteria for treatment failure within the VISUAL trials,[4, 5] it was assumed that patients could not go blind before treatment failure. This was assumed both for the intervention and the comparator. The rate of blindness following treatment failure was then approximated so that the rate of blindness at each cycle in the placebo group was equivalent to the estimate from Dick *et al*.[24] It was not considered clinically reasonable that a dexamethasone implant would prevent all cases of blindness during treatment, but it was deemed equally unreasonable to assume that it would prevent no cases of blindness. In the light of absence of evidence around this parameter, the AG sampled from a uniform distribution between 0 and 1 within the PSA and used the mean of this distribution (0.5) for the deterministic analysis. Therefore, the AG assumed that half of the cases of blindness in this group would be avoided for the period in which the treatment effect is applied (30 weeks in the base case). It was assumed that patients in the comparator group would have the same blindness rate as in the general population.

The AG heard from clinicians that around 20%-30% of patients with uveitis remain unilateral and that patients treated with dexamethasone are more likely to be unilateral. The AG assumed that patients that remained unilateral would not go blind and therefore the rate of blindness in the target population of dexamethasone would be lower than in the general population and this is turn lower than in the target population of adalimumab. For the base case, the AG assumed that in the general population, 25% of patients would remain unilateral whilst in the dexamethasone target population 30% of patients would remain unilateral. For adalimumab, the proportions of patients with unilateral uveitis as reported in VISUAL I (9.2%)[4] and VISUAL II (4.4%)[4, 5] were used for active and inactive patients respectively. The blindness rate for bilaterals was adjusted by dividing the rate by the proportion of bilaterals in the general population. The incidence of blindness in each analysis was adjusted by multiplying the rate of blindness for bilaterals by the proportion of bilateral patients in each population.

Adverse events

One of the key drivers for new treatment options is the substantial adverse event profile of existing treatments, which reduce HRQoL and incur treatment costs. In addition, treatment with adalimumab and dexamethasone is associated with adverse events. Given that the main outcome measures being used from the clinical trials are VFQ-25 and EQ-5D, it is assumed that these will capture the quality of life impacts associated with adverse events during the period in which the treatment is provided. The incidence of AEs from the trials was therefore used to calculate only the additional costs associated

with their management. As such, adverse events included within the model are limited to those where the cost of treatment is substantial. Based upon advice from the clinical experts to the AG, adverse events associated with substantial costs of treatment are: cataract, raised IOP, glaucoma, serious infections; hypertension; fractures; and diabetes.

There is no clinical rationale for the adverse events associated with corticosteroids to differ between study arms because the usage is si milar between the arms within the trials. Therefore, whilst diabetes and osteoporosis are associated with substantial costs, there are no real differences in incidence between the arms of the trials. Within the exploratory analysis assessing the impact of greater corticosteroid use in the comparator groups, the proportion of patients with these adverse events was increased according to their incidence in the MUST trial.[74]

The probabilities for AEs per cycle (are shown in Table 32) were calculated based on the incidence in the trials and the mean follow-up time of each trial

Table 32: Probability of AEs per cycle

			Active uveitis		Inactive uveitis		
	DEX 700	**LCP(H)**	**ADA**	**LCP(VI)**	**ADA**	**LCP(VII)**	**SS&I**
Raised IOP	0.019	0.005	0.002	0.002	0.001	0.001	0.001
Cataract	0.016	0.011	0.002	0.002	0.001	0.003	0.008
Glaucoma	0.000	0.002	0.001	0.000	0.000	0.000	0.001
Hypertension	0.002	0.003	0.002	0.001	0.003	0.003	0.002
Serious infections	0.000	0.000	0.003	0.003	0.001	0.001	0.000
Fracture	0.000	0.000	0.000	0.000	0.000	0.000	0.002
Diabetes	0.000	0.000	0.000	0.000	0.000	0.000	0.001

DEX 700: Dexamethasone 0.7mg; ADA: Adalimumab; SS&I: Systemic steroids and immunosuppressants: LCP(H): Limited current practice based on HURON; LCP(VI): Limited current practice based on VISUAL I; LCP(VII): Limited current practice based on VISUAL II; IOP: Intraocular pressure

Quality of life

Estimating the relationship between VFQ-25 and EQ-5D

The AG considered the published studies for mapping VFQ-25 to EQ-5D included in the database of mapping studies by Dakin.[103] However, none of the published mapping studies were based on a uveitis population, and considering that the AG had access to the VFQ-25 and EQ-5D patient-level data at baseline of the HURON study, the AG decided to fit a new mapping model. The AG used the approach that produced the best fit according to Browne et al.[104] (ordinary least squares) and it noticed that the mapping resulted in similar coefficient values to those presented by Payakachat et al.[105] which used an

alternative modelling method (censored least absolute deviation). The mapping is used for all the analyses involving dexamethasone, within the exploratory analyses comparing the interventions with current practice as provided in MUST,[74] and within a sensitivity analysis for adalimumab.

The patient-level data from HURON were used to test for a correlation between VFQ-25 and EQ-5D baseline. The scatter plot is presented in

Figure 16. A linear regression model was fitted to the data to predict EQ-5D utilities from the VFQ-25. One regression model was fitted to all three arms of the HURON trial; sham, dexamethasone implant 0.35mg; dexamethasone implant 0.7mg, in order to maximise the sample size for the regression analysis. The underlying assumption was that the relationship between VFQ-25 and EQ-5D utility would be independent of treatment. The fitted regression used in the economic model is:

$$EQ\text{-}5D\ utility = 0.4454059 + VFQ\text{-}25\ score * 0.0051322$$

It is recognised that a linear model is not bounded and is likely to have poor performance for utility values at the extremes. However, given that the mapping is only used for means, no extremes values are used. Alternative non-linear models (eg. quadratic regression) were also tested but did not significantly improve the fit to the data. The variance-covariance matrix of the slope and the intercept of the regression model is presented in Table 33. To represent the uncertainty of the regression model, the matrix was u sed to sample the two coefficients of the regression model in the PSA.

Figure 16: The relationship between VFQ-25 and EQ-5D based on patient-level data from the HURON trial

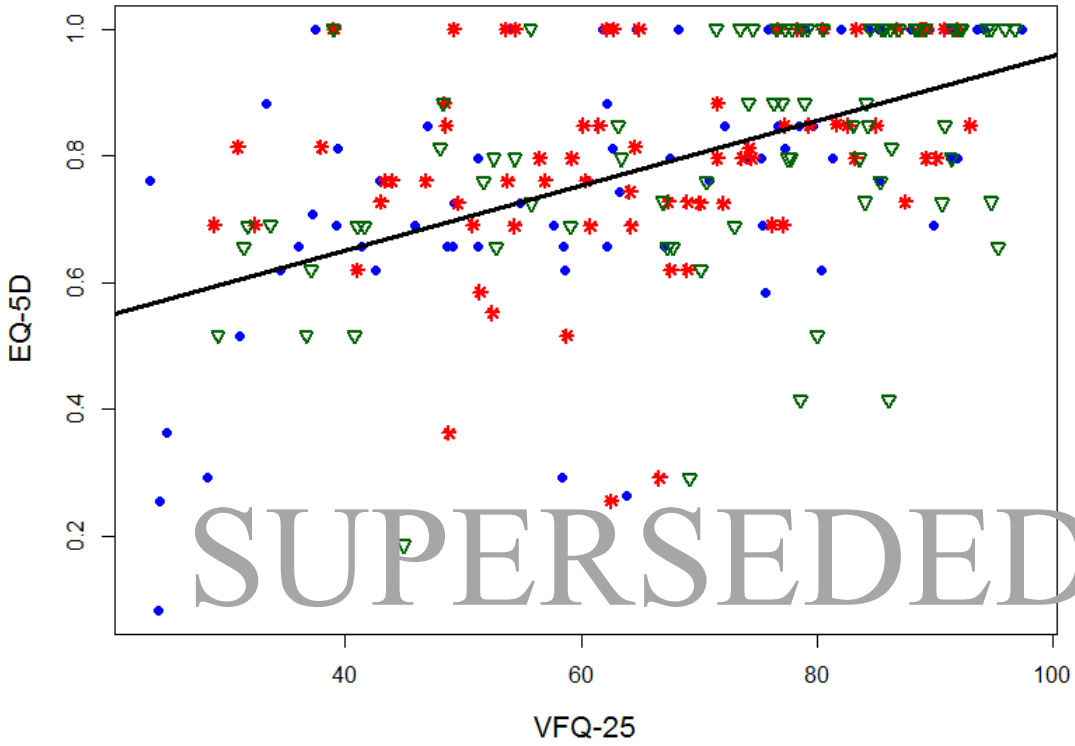


Table 33: Variance-covariance matrix of the intercept and the covariate of the regression model

Intercept	1.75E-03	
VFQ	-2.42E-05	3.63E-07
	Intercept	**VFQ**

The baseline utilities, i.e. the utilities for patients at week 0, were estimated based upon the patient level data from each trial: HURON[7] for dexamethasone and its comparator (LCP(H)), VISUAL I for adalimumab and its comparator in active patients (LCP(VI)), and VISUAL II in for adalimumab and its comparator in inactive patients (LCP(VII)).[4, 5] In HURON, the baseline utilities and visual acuity were substantially different between the sham and the dexamethasone arms (visual acuity was 71.3 for the sham arm and 63.7 for the DEX 700 arm). Clinical advisors to the AG were asked to consider whether the baseline difference in both utility and visual acuity are reasonably due to random variation. All three experts agreed that a difference in visual acuity of 10 letters or more is considered to be clinically significant and could be due to random variation below this level, and therefore it is plausible that the

differences at baseline were due to random variation. The baseline utilities were not varied to represent any population subgroups because these data were not available from the trials. The impact of changing the baseline utility has been assessed within the univariate sensitivity analysis; however, this analysis assumes that the relative treatment effect remains the same. This is unlikely to be the case for subgroups with differing baseline utilities such as patients with unilateral or bilateral uveitis. However, there is no evidence from the trials around outcomes for these subgroups which would enable a robust subgroup analysis.

Estimating utility over time

VFQ-25 data from each follow-up point within the HURON trial[7] (weeks 0, 8, 16, 26) and EQ-5D data from each follow-up point of the VISUAL trials[4, 5] (weeks 0, 1, 4, 6, 8, 12, 16, 20, 24, 27, 32, then every four weeks until week 80) were used to estimate the change in utility for each treatment group over the time period of the trials. These were adjusted according to the average baseline utilities but maintaining the change from baseline in each arm.

When comparing adalimumab with its comparator, for patients who fail and hence discontinue treatment, it was assumed that utility returns to the baseline utility score, adjusted for any reduction in utility associated with age. For patients who receive adalimumab beyond the duration of the trial (80 weeks), it was assumed that their utility remains constant after the last follow-up point until treatment discontinuation. This utility is based on the mean of the last six months of data (see Figure 18 and Figure 19). When comparing dexamethasone with its comparator, the AG assumed that the utility of patients who received dexamethasone would drop to that of its comparator after the duration of the treatment effect. Within the base case analysis, the treatment effect was assumed to be 30 weeks long (four weeks longer than the trial period). Within the sensitivity analyses, the utility is assumed to decrease to the base line utility score over varying time periods.

Figure 17, Figure 18 and Figure 19 present the predicted mean utility values over time, excluding any adjustments for blindness, for dexamethasone versus LCP(H) for active patients, adalimumab versus LCP(VI) for active patients, and adalimumab versus LCP(VII) for inactive patients, respectively.

Figure 17: Mean utilities for dexamethasone versus LCP(H) for active patients over time

[redacted]

Figure 18: Mean utilities for adalimumab versus LCP(VI) for active patients over time

[redacted]

Figure 19: Mean utilities for adalimumab versus LCP(VII) for inactive patients over time

Age adjustments to utility were based on the regression equation reported by Ara and Brazier.[96] Age-related utility was calculated using the following formula:

$$Utility = A \times (Age) + B \times (Age \times Age) + C$$

$$where\ A = -0.0001728,\ B = -0.000034,\ C = 0.9584588$$

The ratio between the utility for the general population at 44 years of age and that of the mean cohort age at each cycle was applied within the model.

Adverse events

Given that the main outcome measures being used from the clinical trials are VFQ-25 and EQ-5D, it is assumed that these will capture the quality of life impacts associated with adverse events during the period in which the treatment is provided.

Utility associated with blindness

There were two studies of utilities associated with blindness based in the UK,[1,2, 106] which the AG thought to be the best sources of evidence. Both studies have been used within previous NICE appraisals.[107-111] Czoski-Murray *et al.* used contact lenses to simulate blindness associated with macular degeneration,[102] whilst Brown *et al.*[106] estimated utility according to valuations by patients with a range of conditions associated with blindness. The AG used the time trade-off values reported in these studies. Each study provided utilities for different levels of blindness, and the AG calculated a weighted average based on the number of patients within the studies falling into each category. This assumes that patients with uveitis would have a similar distribution for the severity of blindness. The study by Czoski-Murray *et al.* was used in the base case analysis as it was based on public valuations of utility; however, it does not provide utilities for the worst states of blindness and may therefore underestimate the overall utility associated with blindness. This resulted in a utility associated with blindness of 0.38. Uncertainty around this parameter was modelled using the variance-covariance matrix provided within the study. The utility estimated from the study by Brown *et al.*[106] (0.57) was employed within sensitivity analysis.

Resource use and costs

Treatment costs

The cost of adalimumab, dexamethasone, immunosuppressants and corticosteroids were based on the latest drug tariff.[112] Drug acquisition costs included within the model are presented in Table 34..

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Table 34: Drug acquisition costs

Drug	Dose	Brand name	6-monthly cost
Adalimumab	40 mg q2w	Humira	£4578
Dexamethasone	One 0.7 mg implant	Ozurdex	£870
Mycophenolate mofetil	1g twice daily	N/A	£136
Methotrexate	15mg weekly	N/A	£16
Cyclosporine	2mg per kg twice daily	N/A	£985
Azathioprine	1mg per kg daily	N/A	£27
Systemic prednisolone	7.5 mg daily	N/A	£12

The cost of treatment with immunosuppressants was calculated separately for each comparison (dexamethasone versus LCP(H), adalimumab versus LCP(VI), adalimumab versus LCP(VII)) as a weighted average of myophenolate mofetil, methotrexate, cyclosporine and azathioprine, based upon their usage in the relevant trial (HURON, VISUAL I, VISUAL II).[4, 5, 7]

The two arms of each clinical trial are similar in terms of the use of corticosteroids and other medications, where reported. There is, however, an imbalance in the use of rescue therapy within the HURON study. The CSR states that the proportions of patients who received rescue therapy, which involved systemic and local corticosteroid use and immunosuppressants, in the dexamethasone arm and the sham arm were 22.1% and 38.2%, respectively.[58] Based upon the patient-level data from HURON, the largest imbalance is in the provision of immunosuppressants as rescue therapy; these therapies are also more costly than corticosteroids. Of those patients who were not already taking immunosuppressants at baseline, only one patient from the dexamethasone arm (1.3%) received an immunosuppressant, whilst eight patients in the sham arm (10.5%) received an immunosuppressant. Of these, three patients received an immunosuppressant for one to two months, and the remaining five patients did not stop immunosuppressant use within the trial period. This suggests that dexamethasone may reduce the need for immunosuppressants. The model includes the costs of the additional immunosuppressants provided to the proportion of patients receiving this rescue therapy. The use of corticosteroid rescue therapy within HURON is more similar between the dexamethasone and sham groups (20.7% for dexamethasone versus 27.7% for sham) and they are generally provided for only two to four weeks, based on the patient level data. Given that corticosteroids are inexpensive, this would result in a minimal cost difference between the groups and hence these costs have not been incorporated within the model. Within the base case, all other treatment costs are assumed to be the same between the dexamethasone group and the LCP(H) and the adalimumab group and LCP(VI)/ LCP(VII). An exploratory analysis was undertaken to explore the impact of an increase in the costs and utilities of the comparators.

Administration costs

The dexamethasone implant is assumed to be administered within one outpatient appointment at a cost of £113.42 based on NHS Reference Costs 2014-15 (Minor Vitreous Retinal Procedures, 19 years and over).[113] Adalimumab is assumed to be self-administered; the base case model assumes that 10% of patients will need help from a district nurse to administer the injections, at a cost of £44 based on PSSRU 2015 (district nurse cost per hour).[114] All other treatments would be administered by the patient and therefore there would be no extra costs of administration for corticosteroids or immunosuppressants.

Monitoring costs

The model assumes that all patients would receive monitoring every 6 weeks, irrespective of treatment. Monitoring consists of outpatient visits for visual function monitoring to assess the efficacy of the treatments and to monitor the risk of AEs. The AG assumed that monitoring for AEs was conducted alongside regular visual function monitoring follow-ups. It is also assumed that patients receiving immunosuppressants would receive 6 additional blood monitoring visits annually. Both regular monitoring and blood monitoring appointments are assumed to cost £96.11 based on NHS Reference Costs 2014-15[113] (Outpatient attendance visit, ophthalmology, face to face visit)).

Cost of adverse events

The management of cataract and glaucoma were based upon surgery costs taken from NHS Reference Costs 2014-15.[113] Raised IOP was assumed to be treated with two doses of bimatoprost on average (most patients will need just one but others will need many). Serious infection was assumed to be treated with hospitalisation and was based upon an average of NHS Reference Costs for the infections reported within the VISUAL trials.[4, 5] Treatment for hypertension was based upon the cost of anti-hypertensive treatment taken from the study by Breeze et al.[115]

A focussed search was undertaken in October 2016 to identify costs and utility studies of blindness (see Appendix 1 for Medline search strategy). Free-text terms for blindness, sight or vision loss (in the titles field) were either combined with an economic filter (balance of sensitivity and sensitivity) or sensitive quality of life studies filter. The search was carried out in Medline and Medline in Process (Ovid). The search for cost studies was limited from 2006 until present. Based on this review, the AG considered that the most recent good-quality evidence associated with the costs of blindness are presented within a HTA of treatment for age-related macular degeneration.[116] The costs of each component included within the calculation of the total annual cost of blindness to the NHS and PSS have been updated with the most recent data, as shown in

Table 35.

Table 35: Costs of blindness

Component	% of patients receiving service	Cost	Source
Blind registration*	95	£146	Meads *et al.*[117]
Low vision aids*	33	£191	Meads *et al.*[117]
Low vision rehabilitation*	11	£329	Meads *et al.*[117]
Depression	39	£2,378	McCrone *et al.*[118]
Hip replacement	5	£4,086	NHS Reference costs 2014-2015[113]
Community care	6	£281	PSSRU 2015[114], social care for older people
Residential care†	30	£21,732	PSSRU 2015[114], private residential care
Annual total		£7,659	

*one-off
† 30% of residents pay themselves

Fracture and diabetes have been shown to be the largest costs associated with the long-term use of corticosteroids.[33] The cost of fracture was based upon evidence from a HTA monograph by Davis *et al*. and includes hospitalisations, Accident and Emergency (A&E) visits, referrals, prescriptions and GP contacts.[119] The cost of diabetes was based upon the annual hospitalisation costs from the UKPDS study, which is the largest study of the costs of diabetes and its complications in the UK,[120] and the treatment costs from Breeze et al.[115] Table 36 summarises the resource use and costs associated with the adverse events included in the model.

Table 36: The resource use and costs associated with the included adverse events

Adverse event	Resource use	Cost	Frequency	Source
Cataract	Cataract surgery	£852.40	One-off cost	NHS Reference costs 2014-15[113]
Raised IOP	Treatment with two doses of bimatoprost	£23.42	One-off cost	BNF, 2016[112]
Glaucoma	Glaucoma surgery	£581.25	One-off cost	NHS Reference Costs 2014-15[113]
Serious infection	Hospitalisation	£5,940.50	One-off cost	NHS Reference Costs 2014-15[113]
Hypertension	Anti-hypertensive prescription	£7.04	One-off cost	Breeze et al.[115]
Permanent blindness	See Table 35 above	£237	Transition	See Table 35 above
		£7,659	Annual	

Fracture	Hospitalisations, accident and emergency visits, referrals, prescriptions and GP contacts	£2,116.17 to £6,022.62 depending on age and gender	One-off fracture cost	Davis et al.[119]
Diabetes	Diabetes treatment and hospitalisation for complications of diabetes	£1,521.46	Annual	Alva et al.,[120] Breeze et al.[115]

Corticosteroid sparing

An important reason for developing new technologies is because existing treatments for non-infectious uveitis are associated with substantial adverse effects. In particular, long-term high dose systemic corticosteroid use is associated with significant morbidity including glaucoma, raised blood pressure, diabetes and osteoporosis.[45, 46] Ideally, corticosteroid sparing benefits would be taken into account in the comparison with current treatment. However, the VISUAL trials do not allow corticosteroid use in either arm following the initial corticosteroid boost and taper, [4, 5] and the HURON trial suggests that there is minimal difference in corticosteroid usage between the arms of the trial.[7] If corticosteroid usage is higher in clinical practice than in the trials, then the effectiveness of the comparator may also increase. Corticosteroid sparing treatment is considered only within the exploratory analyses, where the comparator is based on the MUST trial.

Remission

Based on advice received from clinical advisors to the AG, an additional state was added to the model to reflect the possibility of patients achieving remission after a stable period, for example after two years on adalimumab. This would mean that patients would discontinue treatment upon achieving remission, but continue to experience the benefits of adalimumab until they were predicted to fail treatment from the extrapolated survival curves. Given that there is no evidence around this, within the base case we assumed that no patients would be taken off treatment due to remission; however alternative assumptions around continued benefit following discontinuation due to remission were considered within the exploratory analyses.

Mortality

Mortality rates within the model were assumed to reflect those of the general population, based on the most recent Office for National Statistics life tables for England, 2013-2015.[121]

The model assumes that adverse events have no impact on mortality, although it is recognised that in practice diabetes, osteoporosis, and blindness would have some impact on mortality.

6.2.1.4 Model evaluation methods

The cost-effectiveness results for dexamethasone and adalimumab versus limited current practice are presented based on both the probabilistic and deterministic versions of the model. Five thousand probabilistic samples were run to estimate the expected costs and QALYs. Uncertainty surrounding incremental costs, outcomes and cost-effectiveness was represented using cost-effectiveness acceptability curves (CEACs) and cost-effectiveness planes. It should however be noted that the uncertainty analysis is likely to underestimate the true uncertainty surrounding the cost-effectiveness of each option due to the numerous structural uncertainties associated with the model that are not captured within the PSA. A range of exploratory scenario analyses were undertaken to explore the sensitivity of the model results to key structural assumptions. A univariate sensitivity analysis was also undertaken to explore the impact of alternative plausible parameters upon the model results. All model results are presented for the entire patient population of interest as evidence did not allow a subgroup analysis to be undertaken; the potential direction of the results for key subgroups such as patients with unilateral and bilateral uveitis are discussed in Section 6.2.3.

Probabilistic sensitivity analysis

In order to assess the uncertainty around the parameter used in the model, the AG defined probability distributions for most parameters using available evidence and undertook PSA. Gamma distributions were used for costs and beta distributions for utility values and probabilities. The relative risk of blindness for dexamethasone was based on a uniform distribution due to the lack of evidence.

Table 37 summarises the input parameters and their base case mean values and distributions used in the PSA. In addition to the parameters listed for

Table 37, beta distributions were defined for utility scores at each time point of each arm, as well as the prevalence of concomitant therapy, and the incidence of AEs and rescue therapy. Multivariate normal distributions were used for the parameters of the survival curves used to determine time to treatment failure. A Dirichlet distribution was used for the weight distribution of the cohort, which determined the mean dose cost of azathioprine and cyclosporine.

Table 37: Model input parameters for the base case scenario

Parameters	Mean	Distribution	Source
Age	44.8	Fixed	
Discount rate (costs and utilities)	3.5%	Fixed	NICE, 2013[97]
Gender (% males)	36.7%	Fixed	HURON[7]
Cycle length	2 weeks	Fixed	
Utilities			
Baseline VFQ-25 for dexamethasone and LCP(H)	66.63	Beta	HURON, data on file
Baseline EQ-5D for patients with active uveitis	[redacted]	Beta	VISUAL I CSR[50, 60]
Baseline EQ-5D for patients with inactive uveitis	[redacted]	Beta	VISUAL II, CSR[59]
Blindness utility	0.38	Multivariate normal (using variance-covariance matrix)	Czoski-Murray *et al* [102]
Regression model for relationship between VFQ-25 and EQ-5D			
Intercept	0.445	Multivariate normal (using variance-covariance matrix in Table 33)	Based on patient-level data from the HURON trial, data on file
Slope	0.005		
Proportion of bilaterals			
General population	75%	Beta	Assumption
Dexamethasone population	70%	Beta	Assumption
Active uveitis population	90.8%	Beta	AbbVie CS[50]
Inactive uveitis population	95.6%	Beta	AbbVie CS[60]
Blindness			
Probability of blindness (annual)	0.0068	Beta	Dick *et al.*[24]
Relative risk of blindness for dexamethasone during 6 month period following implantation	0.5	Uniform	Assumption
Relative risk of blindness for adalimumab whilst on treatment	0	Fixed	Assumption
Remission			
Rate of remission where treatment is stopped but the treatment effect continues	0	Fixed	Assumption
Drug costs			
Dexamethasone 700 mg	£870	Fixed	BNF, 2016[112]
Adalimumab 40mg	£352.14	Fixed	BNF, 2016[112]

Parameters	Mean	Distribution	Source
Prednisolone	£1.24	Fixed	BNF, 2016[112]
Mycophenolate mophetil	£9.31	Fixed	BNF, 2016[112]
Methotrexate	£2.40	Fixed	BNF, 2016[112]
Cyclosporine	£48.50	Fixed	BNF, 2016[112]
Azathioprine	£3.24	Fixed	BNF, 2016[112]
Bimatoprost	£11.71	Fixed	BNF, 2016[112]
Adcal D3	£7.49	Fixed	BNF, 2016[112]
Omeprazole	£1.17	Fixed	BNF, 2016[112]
Administration and monitoring			
Monitoring visit frequency	6 weeks		Jabs et al.[122]
Monitoring visit cost	£96.11	Gamma	NHS Reference costs 2014-15, outpatient attendance, ophthalmology, consultant-led[113]
Dexamethasone implant administration cost	£113.42	Gamma	NHS Reference costs 2014-15, Minor Vitreous Retinal Procedures[113]
% of self-injectors needing district nurse for adalimumab	10%	Beta	TA375[123]
Adalimumab administration cost (patients who need help from a nurse)	£44	Gamma	PSSRU 2015[114], district nurse[113]
AE costs			
Cataract surgery	£852.40	Gamma	NHS Reference costs 2014-15, Phacoemulsification Cataract Extraction and Lens Implant, with CC Score 4+ [113]
Raised IOP	£23.42	Gamma	BNF, 2016[112]
Glaucoma procedure	£581.25	Gamma	NHS Reference costs 2014-15, weighted average of glaucoma procedures
Serious infection	£5,940.50	Gamma	NHS Reference costs 2014-15, average of infection hospitalisations[113] (based on the proportions of each infection in the VISUAL trials[4, 5])
Hypertension	£7.04	Gamma	Breeze et al.[115]
Blindness (transition)	£237	Gamma	See Table 35
Blindness (annual)	£7,659	Gamma	See Table 35
Fracture	£2,116.17-£6,022.62	Gamma	Davis et al.[119]
Diabetes	£1,521.46	Gamma	Alva et al.,[120] Breeze et al.[115]

Exploratory sensitivity analyses

A number of exploratory analyses were undertaken to explore the uncertainties within the model. Whilst there is a lack of evidence to fully inform these exploratory analyses, their aim is to provide an indication of the impact of alternative assumptions on the results.

1) A greater proportion of patients are treated with immunosuppressants and corticosteroids in the comparator groups

In clinical practice, it would be expected that a higher proportion of patients would receive systemic therapy. This would result in greater efficacy associated with the comparator, with a higher adverse event rate and higher costs.

As discussed within Section 5.2.3, it was not possible to undertake an NMA to compare dexamethasone or adalimumab with an alternative comparator which might be more representative of current practice. However, the comparator arm of the MUST study[74] (identified within the systematic review), is made up of patients who received systemic corticosteroids, supplemented in 86% of the cases with immunosuppressants and is thought by the clinical experts to the AG to be reasonably representative of clinical practice. Hence, this has been used to inform an exploratory analysis. This exploratory analysis was not undertaken for patients with inactive uveitis because the MUST trial includes only patients with active uveitis. For active patients, data from the comparator arm of the MUST trial was used relating to: (a) an estimate of the total proportion of patients receiving (i) corticosteroids and (ii) immunosuppressants in order to estimate costs; (b) an estimate of the HRQoL of patients, and; (c) the rates for any adverse events associated with substantial resource use. With respect to the total proportion of patients receiving corticosteroids and immunosuppressants, it is unclear from the MUST trial publications exactly which immunosuppressants were used,[74] hence the composition is assumed to be the same as that for VISUAL I.[4] It should be noted that using the data from the MUST trial without performing any formal statistical analysis assumes that the trial population is comparable with the populations within VISUAL and HURON and does not include any measure of uncertainty around the comparison.

Within the base case analysis, HRQoL is assumed to return to baseline following treatment failure with adalimumab or after six months following dexamethasone implantation. Given that the comparator arm patients are able to receive immunosuppressants and corticosteroids, it is assumed within this exploratory analysis that patients treated with adalimumab or dexamethasone are also able to receive immunosuppressants and corticosteroids. Therefore, the effectiveness of dexamethasone and adalimumab is expected to increase as well as the effectiveness of the comparator.

The analysis assumes that treatment with prednisolone includes Adcal D3 (£47.58) and omeprazole 20mg once daily (£15.25) concomitant therapy.

2) Incidence and HRQoL impact of blindness

Since there is limited evidence around the rate of legal blindness for this patient group, and there is no evidence around the impact of treatment upon this rate, the AG performed exploratory analyses around these parameters. This was done by varying the rate of legal blindness in patients with uveitis who are treated with (limited) current practice (from 0 to 0.0374) based upon alternative sources[16, 25] (See 'permanent blindness' section), and the relative risk of legal blindness cases avoided owing to the effect of treatments (from 0 to 1).

3) Patients who go into remission due to adalimumab treatment

A proportion of patients who continue treatment with adalimumab may achieve remission. The base case analysis assumes that these patients would continue to receive adalimumab until treatment failure; however, the clinical advisors to the AG suggested that after around two years of stable disease, patients may no longer require treatment but because they are in remission they may maintain the same level of HRQoL as that whilst on treatment. This sensitivity analysis therefore assesses the impact of assuming that, after two years on treatment, a range of proportion of patients (0 – 1) would no longer receive adalimumab, but their HRQoL would only decrease due to age, until they die due to other causes.

4) Using the VFQ-25 data from the VISUAL trials of adalimumab to map to EQ-5D utility data

This sensitivity analysis assesses the impact of using the EQ-5D data directly: (a) adjusting for the baseline differences between the placebo and adalimumab arms of the trials by using the average baseline EQ-5D from the trial, and; (b) adjusting the baseline utilities to be equivalent to those from the HURON trial to be more representative of UK utility values.

5) Extrapolation of time to treatment discontinuation for adalimumab

The impact of using alternative plausible parametric distributions (Weibull, Gompertz) for time to treatment discontinuation was explored.

6) Varying the time period over which the utility decreases to that of baseline after treatment

The treatment effect beyond six months for dexamethasone and beyond treatment discontinuation for adalimumab is unknown. Within the base case, patients receiving dexamethasone are assumed to take four weeks to return to baseline utility beyond the trial follow-up of six months. HRQoL for patients receiving adalimumab is assumed to return to baseline immediately upon treatment discontinuation. Within this exploratory analysis, for dexamethasone this time period is varied from 0 to 8 weeks, and for adalimumab this time period is increased to four weeks.

Univariate sensitivity analyses

Each parameter within the base case was varied to assess its impact upon the model results, as shown within

Table 38.

Table 38: Univariate sensitivity analyses

Parameters	Mean	Lower value	Upper value	Source
Utilities				
Baseline utility	0.79	0.77	0.80	HURON trial IPD, data on file
	[redacted]	[redacted]	[redacted]	VISUAL I CSR[50, 60]
	[redacted]	[redacted]	[redacted]	VISUAL II, CSR[59]
Blindness utility	0.35	0.28	0.42	Czoski-Murray *et al.* [102]
Administration and monitoring				
Monitoring visit frequency	6 weeks	4 weeks	8 weeks	Jabs et al.[122]
Monitoring visit cost	£96.11	£77.27	£114.95	NHS Reference costs 2014-15, outpatient attendance, ophthalmology, consultant-led[113]
Dexamethasone implant administration cost	£113.42	£91.15	£135.65	NHS Reference costs 2014-15, Minor Vitreous Retinal Procedures[113]
% of self-injectors needing district nurse for adalimumab	10%	0%	20%	TA375[123]
Adalimumab administration cost (patients who need help from a nurse)	£44	£29.96	£44.56	PSSRU 2015[114]
AE costs				
Raised IOP	£23.42	£11.71	£46.84	BNF, 2016[112]
Cataract surgery	£852.40	£658.33	£1019.47	NHS Reference costs 2014-15, Phacoemulsification Cataract Extraction and Lens Implant, with CC Score 4+ [113]
Glaucoma procedure	£581.25	£467.32	£695.17	NHS Reference costs 2014-15, weighted average of glaucoma procedures
Hypertension	£7.04	£5.66	£8.42	Breeze et al.[115]
Serious infections	£5,940.50	£4,776	£7,105	NHS Reference costs 2014-15, average of infection hospitalisations[113] (based on the proportions of each infection in the VISUAL trials[4, 5])
Blindness(transition)	£236.95	£191	£283	See Table 35
Blindness(annual)	£7,658.71	£6,158	£9,160	See Table 35

6.2.2 Results

6.2.2.1 Dexamethasone

Base case

The base case results are presented in Table 39. Based on the probabilistic version of the model, a single dexamethasone implant combined with limited current practice as provided in the HURON trial (DEX 700 + LCP(H)) was estimated to produce 0.029 incremental QALYs compared with LCP(H) alone at an additional cost of £573, resulting in an ICER of £19,509 per QALY gained.

Figure 20 presents the cost-effectiveness acceptability curve (CEAC) . Assuming WTP thresholds of £20,000 and £30,000 per QALY gained, the probability that a single dexamethasone implant produces more net benefit than limited current practice is estimated to be 0.35 and 0.64, respectively. The deterministic results were similar to those generated using the probabilistic model (see Table 40) with an estimated ICER of £20,058 per QALY gained for dexamethasone + LCP(H) compared with LCP(H). A breakdown of the results of the deterministic analysis is provided in Appendix 8.

Table 39: Results of the base case analysis comparing dexamethasone vs LCP(H) (probabilistic)

	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER	Probability of cost-effectiveness at WTP threshold	
						£20,000	£30,000
LCP(H)*	14.599	£39,992				0.53	0.28
DEX 700+ LCP(H)*	14.629	£40,565	0.029	£573	£19,509	0.47	0.72

*LCP(H)= Limited current practice, as provided in the HURON trial:25% of patients on anti-inflammatory or immunosuppressant medication.

Table 40: Results of the base case analysis comparing dexamethasone vs LCP(H) (deterministic)

	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER
LCP(H)*	14.613	£39,655			
DEX 700 + LCP(H)*	14.641	£40,235	0.029	£580	£20,058

* LCP(H)= Limited current practice, as provided in the HURON trial:25% of patients on anti-inflammatory or immunosuppressant medication.

The small differences in both costs and QALYs between the two groups mean that the ICER is very sensitive to alternative model parameters and assumptions, as shown within subsequent sensitivity analyses.

Figure 20: Cost-effectiveness acceptability curve of DEX 700 + LCP(H) vs LCP(H)

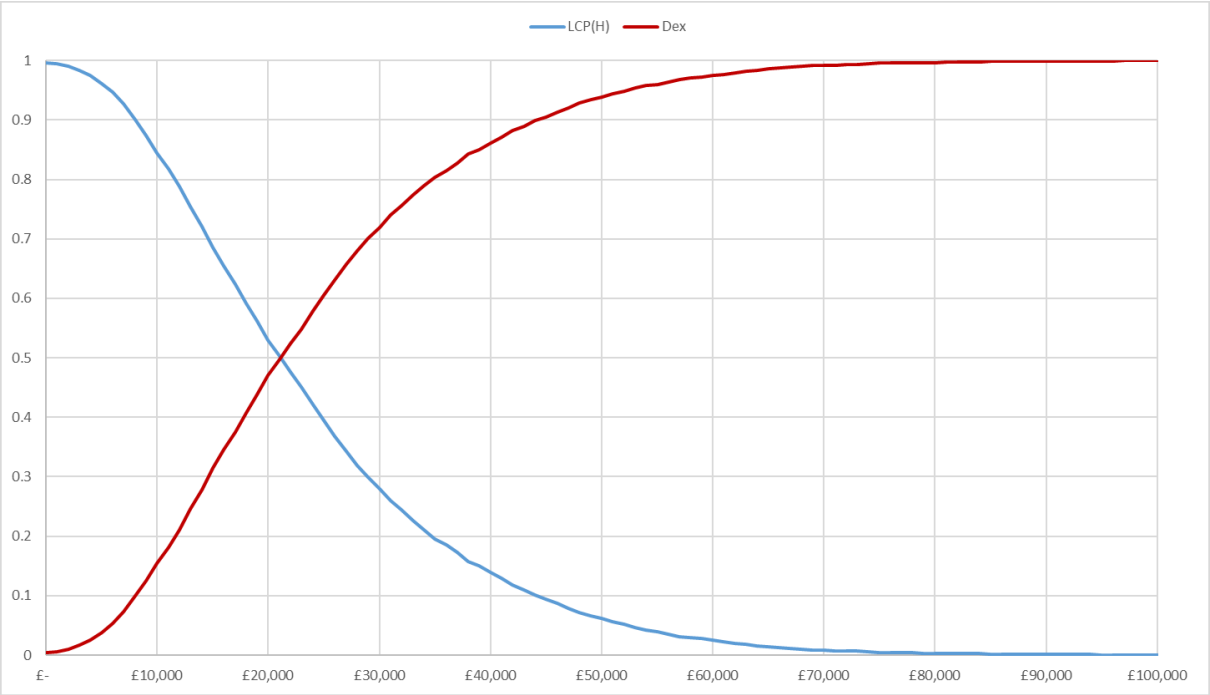
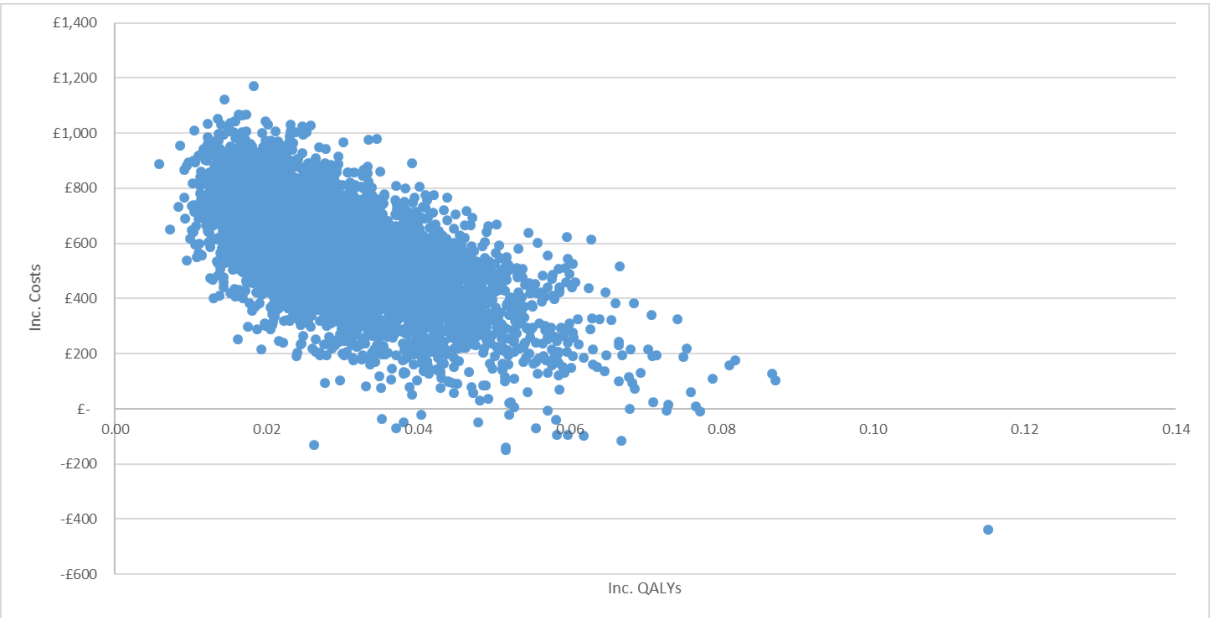


Figure 21 shows the cost-effectiveness scatterplot of dexamethasone + LCP(H) compared with LCP(H). The scatterplot shows that there is a negative correlation between incremental costs and QALYs. The AG believes that this is due to the impact of dexamethasone on blindness being very uncertain and having a strong impact both on QALYs gained and costs. A low relative risk of blindness would lead to increased QALY gains and important costs savings.

Figure 21: Cost-effectiveness plane scatterplot of DEX 700 + LCP(H) vs LCP(H)



Exploratory analyses

Exploratory analysis 1: A greater proportion of patients are treated with immunosuppressants and corticosteroids in the comparator groups

This exploratory analysis suggests that injecting a dexamethasone implant before applying a treatment considered to be current practice (a mix of systemic steroids and immunosuppressants, based on the comparator within the MUST trial[74]) is expected to produce 0.011 additional QALYs at an incremental cost of £216 compared with current practice, resulting in an ICER of £19,899 per QALY gained, as shown in Table 41.

Table 41: Results of exploratory analysis comparing dexamethasone vs current practice (probabilistic)

	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER	Probability of cost-effectiveness at WTP threshold	
						£20,000	£30,000
CP(M)*	15.152	£63,465				0.54	0.45
DEX 700 + LCP(H)† before CP(M)*	15.163	£63,681	0.011	£216	£19,899	0.47	0.55

*CP(M)= Current practice as provided in the MUST trial: all patients on systemic steroids and 86% on systemic immunosuppressants.
†LCP(H)= Limited current practice, as provided in the HURON trial:25% of patients on anti-inflammatory or immunosuppressant medication

Within this exploratory analysis, the total QALYs associated with dexamethasone increases compared with the base case because of the assumption that patients would be able to receive more immunosuppressants and corticosteroids (equivalent to the comparator group) after six months following the dexamethasone implant. The AG notes that the ICER estimated for DEX versus CP(M) is only slightly higher than that of DEX versus LPC(H). The difference would be higher if different rates of blindness had been applied for CP(M) and LCP(H). It is reasonable to assume that CP(M) would lead to a lower incidence of blindness compared with LCP(H) due to the more intensive treatment, but the AG assumed the same rate of blindness for both given the absence of evidence to estimate rates for both.

Exploratory analysis 2: Incidence and HRQoL impact of blindness

The AG analysed the combined impact of different blindness rates based on different sources in the literature and assuming different relative risks for blindness on dexamethasone. As shown in Table 42, the impact of relative risks upon the ICER for dexamethasone plus LCP(H) versus LCP(H) alone is very important and there is no evidence describing the impact dexamethasone will have upon the rate of blindness. The higher the rate of blindness, the greater the impact of the relative risk upon the model results. Based on an assumed rate of blindness from Durrani et al.[16] and a relative risk of 1 (i.e. a dexamethasone implant has no effect on blindness), this leads to an ICER of £56,329 per QALY gained,

whereas dexamethasone dominates if the relative risk is 0.25 or lower based on the same rate of blindness.

Table 42: ICERs of DEX 700 + LCP(H) vs LCP(H) with different blindness rates and RRs of blindness for patients whilst on dexamethasone

		RR of blindness whilst on dexamethasone				
Source	**Rate (annual)**	**0 (no blindness)**	**0.25**	**0.50***	**0.75**	**1 (no effect)**
Assumption	0	£48,937	£48,937	£48,937	£48,937	£48,937
Tomkins-Netzer et al.[25]	0.0038	£17,100	£21,816	£28,089	£36,844	£49,915
Dick et al.[24]*	0.0066	£8,688	£13,314	£20,058*	£30,805	£50,627
Durrani et al.[16]	0.0374	Dominates	Dominates	£557	£10,900	£56,329

*base case

The AG also explored the impact of assuming a different source for the utility for patients following the onset of blindness. The base case uses estimates based on Czoski-Murray et al.;[102] an exploratory analysis was also undertaken using estimates reported by Brown et al.[106] The results of these exploratory analyses are presented in

Table 43, and lead to higher ICERs for dexamethasone plus LCP(H) versus LCP(H) compared with those based on Czoski-Murray et al.[102] (in cases where the rate of blindness is higher than zero and dexamethasone has an impact upon the rate of blindness). This is due to the utility for blindness being lower when estimated based on Czoski-Murray et al.[102] (0.38) compared with that based on Brown et al.[106] (0.57).

Table 43: ICERs of DEX 700 + LCP(H) vs LCP(H) with different blindness rates and RRs of blindness for patients on dexamethasone using utilities from Brown et al.

		RR of blindness on dexamethasone				
Source	**Rate (annual)**	**0 (no blindness)**	**0.25**	**0.50***	**0.75**	**1 (no effect)**
Assumption	0	£48,937	£48,937	£48,937	£48,937	£48,937
Tomkins-Netzer et al.[25]	0.0038	£22,015	£26,972	£32,988	£40,440	£49,915
Dick et al.[24]*	0.0066	£12,108	£17,782	£25,257*	£35,550	£50,627
Durrani et al.[16]	0.0374	Dominates	Dominates	£853	£15,198	£56,329

*base case

In order to explore the impact of the cost of blindness, the AG undertook an analysis using the upper bounds of the 95% confidence intervals for the annual cost of blindness and the cost of the transition to blindness. Table 44 presents the result of these exploratory analyses, which lead to lower ICERs of dexamethasone plus LCP(H) versus LCP(H) compared with the analyses using the mean costs of blindness (in cases where the rate of blindness is higher than zero and dexamethasone has an impact upon the rate of blindness).

Table 44: ICERs of DEX 700 + LCP(H) vs LCP(H) with different blindness rates and RRs of blindness for patients on dexamethasone using a high cost of blindness (upper bound of 95% CI)

		RR of blindness on dexamethasone				
Source	**Rate (annual)**	**0 (no blindness)**	**0.25**	**0.50***	**0.75**	**1 (no effect)**
Assumption	0	£48,937	£48,937	£48,937	£48,937	£48,937
Tomkins-Netzer et al.[25]	0.0038	£15,195	£20,185	£26,822	£36,085	£49,915
Dick et al.[24]*	0.0066	£6,283	£11,174	£18,305*	£29,668	£50,627
Durrani et al.[16]	0.0374	Dominates	Dominates	Dominates	£8,534	£56,329

*base case

For the above analyses, where the annual rate of blindness is set to 0, the results could be used to give an indication around the cost-effectiveness of dexamethasone for patients with unilateral disease (since patients with unilateral disease are unlikely to become legally blind, unless their disease progresses to become bilateral). This results in an ICER of £48,937. It is important to note that the treatment effect may also be different (expected to be reduced) for unilateral patients compared with a pooled group of unilateral and bilateral patients; however there is no evidence available to model this.

Exploratory analysis 6: Varying the time period over which the utility decreases to that of baseline after treatment

The base case assumes that the health-related gain from dexamethasone as measured at the end of the HURON trial (week 26) is maintained for 4 weeks (up to week 30) and then falls to that of the comparator arm. Table 45 shows the impact of varying the treatment effect duration on the cost-effectiveness estimates. The ICER for dexamethasone plus LCP(H) versus LCP(H) varies from £23,341 per QALY gained assuming 26 weeks of treatment effect to £11,282 per QALY gained assuming 42 weeks.

Table 45: Results of exploratory analyses with varying duration of treatment effect on HRQoL (deterministic)

	Total QALYs	**Total costs**	**Inc. QALYs**	**Inc. costs**	**ICER**
LCP(H)	14.613	£39,655			
Dex:26 weeks	14.637	£40,256	0.024	£600	£24,715
Dex:30 weeks*	14.641	£40,235	0.029	£580	£20,058
Dex:34 weeks	14.646	£40,214	0.033	£559	£16,692
Dex:42 weeks	14.655	£40,173	0.043	£518	£12,154

*base case

Univariate sensitivity analyses

The AG explored the impact of different parameters on the results of the model as shown in Table 46

Table 46: Univariate sensitivity analyses for DEX 700 + LCP(H) vs LCP(H). Base case ICER: £20,058 per QALY (deterministic)

Parameters	Base case, lower value, upper value	ICER based on lower value	ICER based on upper value
Utilities			
Baseline utility	0.79, 0.77, 0.80	£20,346	£19,783
Blindness utility	0.38, 0.31, 0.57	£18,551	£25,257
Administration and monitoring	0.35, 0.28, 0.42		
Monitoring visit frequency	6 weeks, 4 weeks, 8 weeks	£20,545	£19,814
Monitoring visit cost	£44, £35.80, £53.03	£19,854	£20,282
Dexamethasone implant administration cost	£113.42, £91.15, £135.65	£19,326	£20,863
AE costs			
Raised IOP	£23.42, £11.71, £46.84	£19,967	£20,240
Cataract surgery	£852.40, £658.33, £1019.47	£19,534	£20,635
Glaucoma procedure	£581.25, £467.32, £695.17	£20,173	£19,931
Hypertension	£7.04, £5.66, £8.42	£20,058	£20,057
Blindness (transition)	£237, £191, £283	£20,061	£20,054
Blindness (annual)	£7,659, £6,158, £9,160	£21,807	£18,308

The model results are generally robust to changes to the values of these parameters. The model is therefore most sensitive to assumptions around the comparator, assumptions around permanent blindness and the duration of the treatment effect.

6.2.2.1 Adalimumab – active uveitis patients

Base case

The base case results are presented in

Table 47. In the base case, adalimumab in combination with limited current practice as provided in the VISUAL I trial (LCP(VI)) was estimated to produce 0.194 incremental QALYs compared with LCP(VI) alone in patients with active uveitis at an additional cost of £18,321, resulting in an ICER of £94,523 per QALY gained. The ICER generated using the deterministic version of the model (£95,506) was similar to that from the probabilistic model (see Table 48). A breakdown of the results of the deterministic analysis is provided in Appendix 8. Figure 22 and shows the CEAC of ADA + LCP(VI) versus LCP(VI) in patients with active uveitis. The AG notes that within the VISUAL I trial both treatment groups included an initial systemic steroid burst which was tapered by week 15 and that around 30% of patients on both arms received systemic immunosuppressants.[4, 5]

Table 47: Results of base case comparing ADA + LCP(VI) vs LCP(VI) in patients with active uveitis (probabilistic)

	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER	Probability of cost-effectiveness at WTP threshold	
						£20,000	£30,000
LCP(VI)*	14.897	£47,776				1.00	1.00
ADA + LCP(VI)*	15.091	£66,098	0.194	£18,321	£94,523	0.00	0.00

*LCP(VI)= Limited current practice, as provided in the VISUAL I trial: initial systemic steroid burst tapered by week 15 and around 30% of patients on systemic immunosuppressants.

Table 48: Results of base case comparing ADA + LCP(VI) vs LCP(VI) in patients with active uveitis (deterministic)

	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER
LCP(VI)*	14.919	£47,186			
ADA + LCP(VI)*	15.110	£65,401	0.191	£18,215	£95,506

*LCP(VI)= Limited current practice, as provided in the VISUAL I trial: initial systemic steroid burst tapered by week 15 and around 30% of patients on systemic immunosuppressants.

Figure 22: Cost-effectiveness acceptability curve of ADA + LCP(VI) vs LCP(VI) in patients with active uveitis

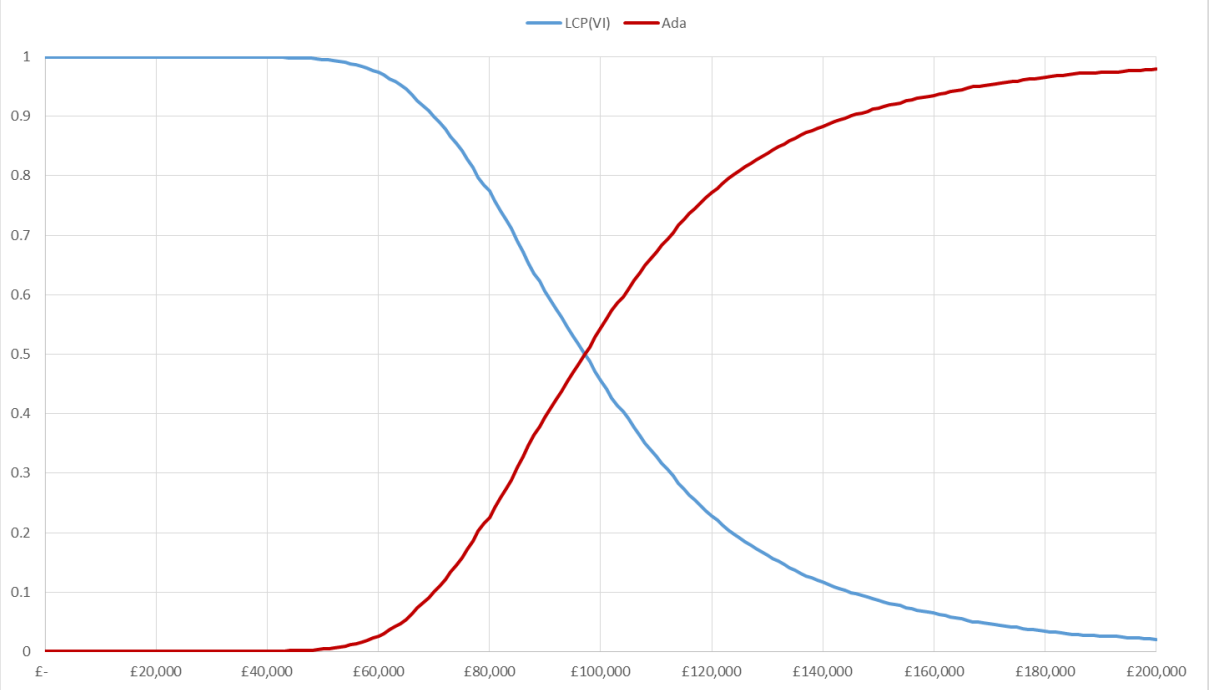
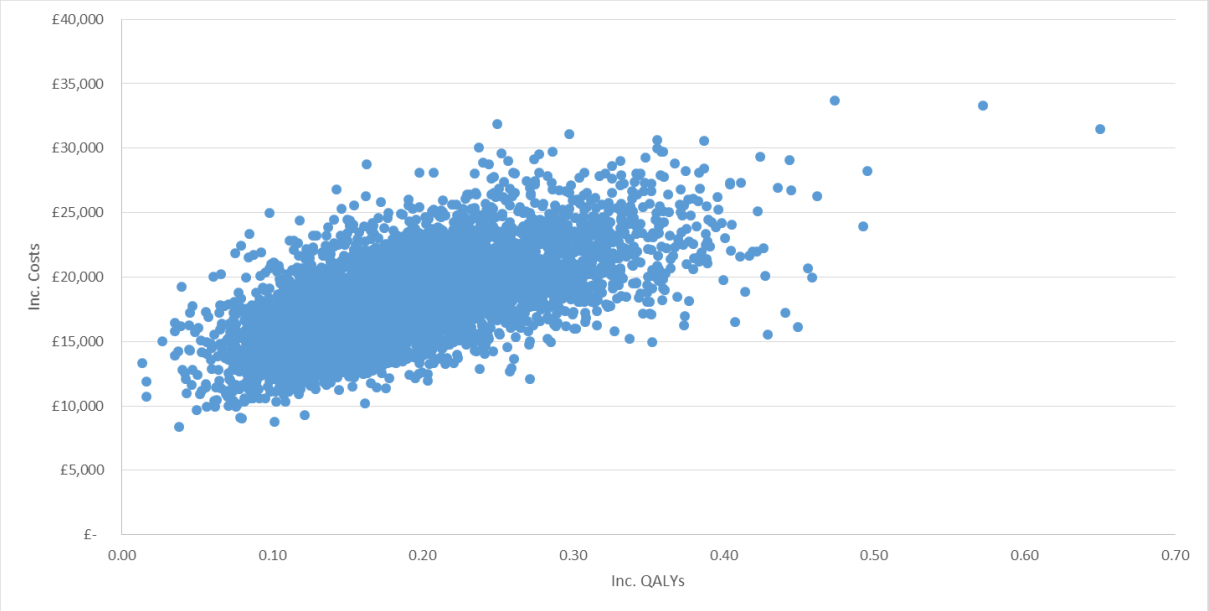


Figure 23 shows the cost-effectiveness plane of ADA + LCP(VI) versus LCP(VI). The scatterplot shows that there is a positive correlation between incremental costs and QALYs. The AG believes this is due to longer adalimumab treatments leading to more QALYs but also incurring important additional costs.

Figure 23: Cost-effectiveness plane scatterplot of ADA + LCP(VI) vs LCP(VI) in patients with active uveitis



Exploratory analyses

Exploratory analysis 1: A greater proportion of patients are treated with immunosuppressants and corticosteroids in the comparator groups

The AG undertook an exploratory analysis (Table 49) whereby patients who fail adalimumab are assumed to receive a treatment that the AG considered was representative of current practice, a mix of systemic steroids and immunosuppressants based on the MUST trial[74] (CP(M)). The analysis shows that ADA + LCP(VI) before CP(M) is expected to produce 0.0159 additional QALYs at an incremental cost of £17,183 compared with CP(M), resulting in an ICER of £109,044 per QALY gained, as shown in Table 49.

Table 49: Results of exploratory analysis of ADA + LCP(VI) before CP(M) vs CP(M) alone (probabilistic)

	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER	Probability of cost-effectiveness at WTP threshold	
						£20,000	£30,000
CP(M)*	15.655	£66,171				1.00	1.00
ADA + LCP(VI)† before CP(M)*	15.813	£83,355	0.158	£17,183	£109,044	0.00	0.00

*CP(M)= Current practice as provided in the MUST trial: all patients on systemic steroids and 86% on systemic immunosuppressants.
†LCP(VI)= Limited current practice, as provided in the VISUAL I trial: initial systemic steroid burst tapered by week 15 and around 30% of patients on systemic immunosuppressants.

Within this exploratory analysis, the total QALYs associated with the adalimumab group increases compared with those within the base case because of the assumption that more patients would be able to receive immunosuppressants and corticosteroids (equivalent to the comparator group) after adalimumab treatment failure. The AG notes that the ICER estimated for ADA versus CP(M) is only slightly higher than that of ADA versus LPC(VI). The difference would be higher if different rates of blindness had been applied for CP(M) and LCP(VI). It is reasonable to assume that CP(M) would lead to a lower incidence of blindness compared with LCP(VI) due to the more intensive treatment, but the AG assumed the same rate of blindness for both given the absence of evidence to estimate rates for both.

Exploratory analysis 2: Incidence and HRQoL impact of blindness

The AG analysed the combined impact of different blindness rates based on different sources in the literature and assuming different relative risks for patients before treatment failure. As shown in Table 50, the impact of the relative risk of blindness on the ICER for ADA + LCP(VI) versus LCP(VI) in patients with active uveitis is highly influential. The higher the rate of blindness, the greater the impact of the relative risk. Assuming the highest rate of blindness from the literature (based on Durrani et al.[16]) resulted in an ICER for ADA + LCP(VI) versus LCP(VI) of £202,592 per QALY gained assuming a relative risk of 1 (i.e. adalimumab has no effect on blindness), and an ICER of £33,003 per QALY gained assuming a relative risk of 0 (i.e. no patient goes blind before treatment failure relative risk).

Table 50: ICERs of ADA + LCP(VI) vs LCP(VI) with varying blindness rates and RRs of blindness for patients before treatment failure

		RR of blindness before treatment failure				
Source	**Rate**	**0 (no blindness) ***	**0.25**	**0.50**	**0.75**	**1 (no effect)**
Assumption	0	£192,808	£192,808	£192,808	£192,808	£192,808
Tomkins-Netzer et al.[25]	0.0038	£121,908	£134,773	£150,325	£169,503	£193,740
Dick et al.[24]*	0.0066	£95,506*	£110,263	£129,611	£156,077	£194,471
Durrani et al.[16]	0.0374	£33,003	£44,570	£63,587	£100,494	£202,592

*base case

The AG also explored the impact of assuming a different source for the utility for patients following the onset of blindness. The base case uses estimates based on Czoski-Murray et al.;[102] an exploratory analysis was also undertaken using estimates reported by Brown et al.[106] The results of these exploratory analyses are shown in Table 51, and produce higher ICERs for ADA + LCP(VI) versus LCP(VI) compared with those based on Czoski-Murray et al.[102] This is due to the utility for blindness being lower when estimated based on Czoski-Murray et al.[102] (0.38) compared with that based on Brown et al.[106] (0.57).

Table 51: ICERs of ADA + LCP(VI) vs LCP(VI) with varying blindness rates and RRs of blindness for patients before treatment failure using utilities from Brown et al.[106]

		RR of blindness before treatment failure				
Source	**Rate**	**0 (no blindness) ***	**0.25**	**0.50**	**0.75**	**1 (no effect)**
Assumption	0	£192,808	£192,808	£192,808	£192,808	£192,808
Tomkins-Netzer et al.[25]	0.0038	£142,399	£152,827	£164,646	£178,154	£193,740
Dick et al.[24]*	0.0066	£119,012*	£132,539	£148,886	£169,031	£194,471
Durrani et al.[16]	0.0374	£48,876	£63,923	£86,679	£124,952	£202,592

*base case

In order to explore the impact of the cost of blindness, the AG undertook an analysis using the upper bounds of the 95% confidence intervals for the annual cost of blindness and the cost of the transition to blindness. Table 52 presents the result of these exploratory analyses, which leads to lower ICERs of ADA + LCP(VI) versus LCP(VI) compared with the analyses using the mean costs of blindness, except when a blindness rate of 0 or a relative risk before treatment failure of 1 is assumed.

Table 52: ICERs of ADA + LCP(VI) vs LCP(VI) with varying blindness rates and RRs of blindness for patients before treatment failure using a high cost of blindness (upper bound of 95% CI)

		RR of blindness before treatment failure				
Source	**Rate**	**0 (no blindness) ***	**0.25**	**0.50**	**0.75**	**1 (no effect)**
Assumption	0	£192,808	£192,808	£192,808	£192,808	£192,808
Tomkins-Netzer et al.[25]	0.0038	£120,637	£133,725	£149,546	£169,056	£193,712
Dick et al.[24]*	0.0066	£93,765*	£108,775	£128,453	£155,372	£194,422
Durrani et al.[16]	0.0374	£30,187	£41,936	£61,245	£98,713	£202,352

*base case

Exploratory analysis 3: Patients who go into remission due to adalimumab treatment

In the base case, the AG assumed that patients would stay on adalimumab until treatment failure. However, based on clinical advice received by the AG, an additional analysis was undertaken assuming that after two years of successful treatment, a proportion of patients would discontinue treatment due to being in remission and maintain the benefits of treatment. Table 53 presents the results for different annual discontinuation rates for patients who have completed two years of successful treatment. As expected, only the cost of treatment for adalimumab varies with different rates of treatment discontinuation after remission: the cost of adalimumab treatment reduces as the rate of discontinuation increases and therefore so does the ICER for ADA + LCP(VI) versus LCP(VI) in patients with active uveitis. If all patients who had not failed treatment (according to the discontinuation criteria defined in

the VISUAL trials[4, 5]) by two years could discontinue adalimumab and retain the benefits accrued from treatment, the ICER for ADA + LCP(VI) versus LCP(VI) is estimated to be £35,299 per QALY gained.

Table 53: Results of exploratory analysis of patients on remission discontinuing treatment after two years of treatment.

Rate of treatment discontinuation (annual)		Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER
0*	LCP(VI)†	14.919	£47,186			
	ADA + LCP(VI)†	15.110	£65,401	0.191	£18,215	£95,506
0.10	LCP(VI)†	14.919	£47,186			
	ADA + LCP(VI)†	15.110	£60,034	0.191	£12,848	£67,363
0.25	LCP(VI)†	14.919	£47,186			
	ADA + LCP(VI)†	15.110	£57,239	0.191	£10,052	£52,707
1.00	LCP(VI)†	14.919	£47,186			
	ADA + LCP(VI)†	15.110	£53,918	0.191	£6,732	£35,299

*basecase

†LCP(VI)= Limited current practice, as provided in the VISUAL I trial: initial systemic steroid burst tapered by week 15 and around 30% of patients on systemic immunosuppressants.

It should be noted that the clinical advisors to the AG suggest that the treatment failure criteria for the VISUAL trials are more strict than would be used in clinical practice, hence it is possible that a greater proportion of patients would still be receiving adalimumab treatment at two years. However, there is no evidence around the extent of the benefit of adalimumab in these patients.

Exploratory analysis 4: Using the VFQ-25 data from the VISUAL trials of adalimumab to map to EQ-5D utility data

The AG undertook an exploratory analysis using EQ-5D scores mapped from VFQ-25 scores captured in VISUAL I instead of using directly measured EQ-5D scores. This analysis resulted in a higher incremental QALY gain and therefore in a slightly lower ICER for ADA + LCP(VI) versus LCP(VI) compared with the base case (see Table 54).

Table 54: Results of ADA + LCP(VI) versus LCP(VI) in patients with active uveitis using EQ-5D scores captured in VISUAL I

	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER
LCP(VI)*	14.350	£47,186			
ADA + LCP(VI)*	14.546	£65,401	0.196	£18,215	£92,884

*LCP(VI)= Limited current practice, as provided in the VISUAL I trial: initial systemic steroid burst tapered by week 15 and around 30% of patients on systemic immunosuppressants.

Exploratory analysis 5: Extrapolation of time to treatment discontinuation for adalimumab

In order to assess the impact of uncertainty around the extrapolation of time to treatment failure, the AG undertook exploratory analyses using alternative parametric curves (Table 55). The ICER for ADA + LCP(VI) versus LCP(VI) was considerably higher when using a Gompertz distribution (£101,429 per QALY) and a Weibull distribution (£103,369 per QALY) compared with the log normal distribution used in the base case (£95,506 per QALY).

Table 55: Results of ADA + LCP(VI) versus LCP(VI) in patients with active uveitis using different parametric curves to extrapolate time to treatment failure

Parametric curve		Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER
Log normal*	LCP(VI)†	14.919	£47,186			
	ADA + LCP(VI)†	15.110	£65,401	0.191	£18,215	£95,506
Gompertz	LCP(VI)†	14.947	£47,186			
	ADA + LCP(VI)†	15.569	£110,215	0.621	£63,029	£101,429
Weibull	LCP(VI)†	14.917	£47,186			
	ADA + LCP(VI)†	15.031	£58,938	0.114	£11,751	£103,369

*basecase
†LCP(VI)= Limited current practice, as provided in the VISUAL I trial: initial systemic steroid burst tapered by week 15 and around 30% of patients on systemic immunosuppressants

Univariate sensitivity analyses

The AG explored the impact of different parameters on the results of the model, as shown in Table 56

Table 56: Univariate sensitivity analyses for ADA + LCP(VI) versus LCP(VI) in patients with active uveitis. Base case ICER: £95,506 (deterministic)

Parameters	Base case, lower value, upper value	Lower value	Upper value
Utilities			
Baseline utility	[redacted], [redacted], [redacted]	£97,804	£93,419
Blindness utility	0.38, 0.31, 0.57	£88,602	£119,012
Administration and monitoring			
Monitoring visit frequency	6 weeks, 4 weeks, 8 weeks	£95,983	£95,267
Monitoring visit cost	£96.11, £77.27, £114.95	£95,290	£95,744
Adalimumab administration cost (help from a nurse)	£44, £35.80, £53.03	£95,272	£95,763
% of self-injectors needing district nurse for adalimumab	10%, 0%, 20%	£94,253	£96,758
AE costs			
Cataract surgery	£852.40, £658.33, £1019.47	£95,465	£95,551
Glaucoma procedure	£581.25, £467.32, £695.17	£95,487	£95,527
Serious infections	£5,940, £4,776, £7,105	£95,272	£95,763
Hypertension	£7.04, £5.66, £8.42	£95,505	£95,506
Blindness (transition)	£237, £191, £283	£95,510	£95,502
Blindness (annual)	£7,659, £6,158, £9,160	£97,243	£93,769

Of those parameters tested within the univariate sensitivity analysis, as shown in

Table 56, the parameters relating to the baseline utility and the utility of blindness had the greatest impact on the ICER for ADA + LCP(VI) versus LCP(VI). However, the model is most sensitive to assumptions around the comparator, assumptions around permanent blindness and the proportion of patients who would discontinue treatment due to achieving remission and maintain the benefits of treatment.

6.2.2.3 Adalimumab – inactive uveitis patients

Base case

In the base case, adalimumab plus limited current practice as provided in VISUAL II trial (LCP(VII)) was estimated to produce 0.118 incremental QALYs compared with LCP(VII) alone at an extra cost of £37,432, resulting in an ICER of £317,547 per QALY gained in patients with inactive uveitis, as shown in Table 57. The deterministic analysis produced a slightly lower ICER (£321,405) as shown in Table 58. A breakdown of the results of the deterministic analysis are provided in Appendix 8. Figure 24 and shows the CEAC and cost-effectiveness plane of ADA + LCP(VII) versus LCP(VII) in patients with inactive uveitis. Figure 25 shows the cost-effectiveness plane scatterplot of ADA + LCP(VII) versus LCP(VII) in patients with inactive uveitis. The scatterplot shows a positive correlation between incremental costs and QALYs as was the case for patients with active uveitis. However, in patients with inactive uveitis, the comparator was more effective than the intervention arm. The AG notes that around 47% of patients in both arms received systemic immunosuppressants.

Table 57: Results of base case comparing ADA + LCP(VII) versus LCP(VII) in patients with inactive uveitis (probabilistic)

	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER	Probability of cost-effectiveness at WTP threshold	
						£20,000	£30,000
LCP(VII)*	15.221	£48,642				1.00	1.00
Ada + LCP(VII)*	15.339	£86,074	0.118	£37,432	£317,547	0.00	0.00

*LCP(VII)= Limited current practice, as provided in the VISUAL II trial: on systemic steroids at baseline tapered by week 19 and around 47% of patients on systemic immunosuppressants.

Table 58: Results of base case comparing ADA + LCP(VII) versus LCP(VII) in patients with inactive uveitis (deterministic)

	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER
LCP(VII)*	15.244	£48,111			
Ada + LCP(VII)*	15.361	£85,462	0.116	£37,351	£321,405

*LCP(VII)= Limited current practice, as provided in the VISUAL II trial: on systemic steroids at baseline (10-35 mg/day) tapered by week 19 and around 47% of patients on systemic immunosuppressants.

Figure 24: Cost-effectiveness acceptability curve of ADA + LCP(VII) versus LCP(VII) in patients with inactive uveitis

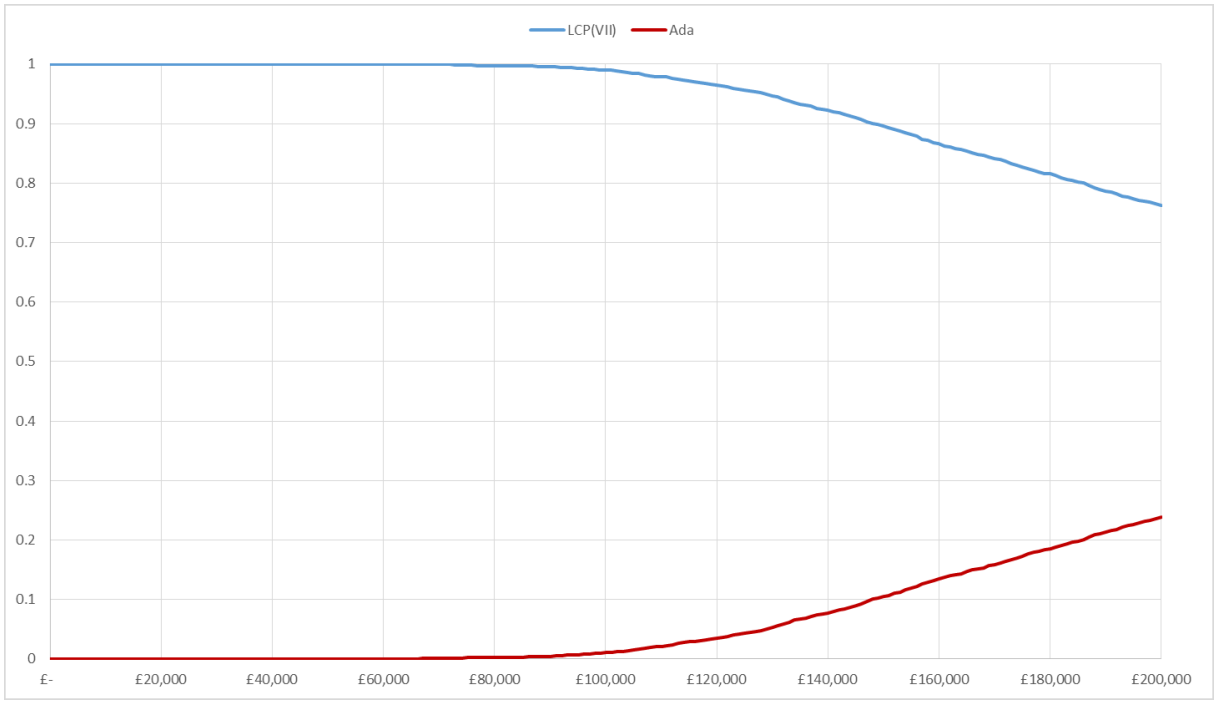
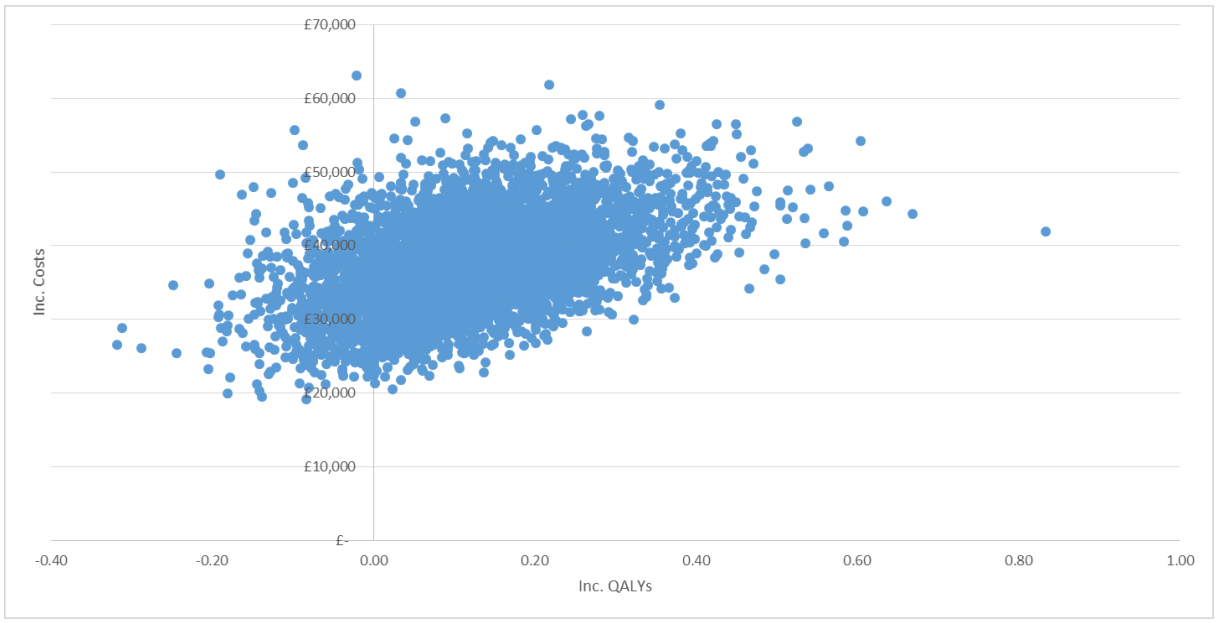


Figure 25: Cost-effectiveness plane scatterplot of ADA + LCP(VII) versus LCP(VII) in patients with inactive uveitis



Exploratory analyses

Exploratory analysis 2: Incidence and HRQoL impact of blindness

The AG analysed the combined impact of different blindness rates based on different sources in the literature and assuming different relative risks for patients before treatment failure. As shown in Table 59, the impact of relative risks in the ICER for ADA + LCP(VII) versus LCP(VII) in patients with inactive uveitis is very important. The higher the rate of blindness, the greater the impact of the relative risk. Assuming the highest rate of blindness from the literature (based on Durrani et al.[16]) results in an ICER for ADA + LCP(VII) versus LCP(VII) of £7,411,362 per QALY gained assuming a relative risk of 1 (no effect on blindness), but an ICER of £85,544 per QALY assuming no patient goes blind before treatment failure (a relative risk of 0).

Table 59: ICERs of ADA + LCP(VII) versus LCP(VII) with varying blindness rates and RRs of blindness for patients before treatment failure

		RR of blindness before treatment failure				
Source	**Rate**	**0 (no blindness)***	**0.25**	**0.50**	**0.75**	**1 (no effect)**
Assumption	0	£4,814,459	£4,814,459	£4,814,459	£4,814,459	£4,814,459
Tomkins-Netzer et al.[25]	0.0038	£527,056	£679,863	£956,162	£1,606,857	£4,988,973
Dick et al.[24]*	0.0066	£321,405*	£420,805	£607,928	£1,089,865	£5,133,625
Durrani et al.[16]	0.0374	£85,544	£112,594	£167,837	£331,006	£7,411,362

*base case

The AG also explored the impact of assuming a different source for the utility for patients following the onset of blindness. The AG used the estimates based on Czoski-Murray et al.[102] in its base case but undertook exploratory analyses using Brown et al.[106] Results of these exploratory analyses are shown in Table 60, and feature higher ICERs for ADA + LCP(VII) versus LCP(VII) compared with those based on Czoski-Murray et al.[102] This is due to the utility for blindness being lower when estimated based on Czoski-Murray et al.[102] (0.38) compared with that based on Brown et al.[106] (0.57).

Table 60: ICERs of ADA + LCP(VII) versus LCP(VII) with varying blindness rates and RRs of blindness for patients before treatment failure using utilities from Brown et al.

		RR of blindness before treatment failure				
Source	**Rate**	**0 (no blindness)***	**0.25**	**0.50**	**0.75**	**1 (no effect)**
Assumption	0	£4,814,459	£4,814,459	£4,814,459	£4,814,459	£4,814,459
Tomkins-Netzer et al.[25]	0.0038	£821,798	£1,040,149	£1,414,808	£2,206,843	£4,988,973
Dick et al.[24]*	0.0066	£514,958*	£665,947	£940,350	£1,593,079	£5,133,625
Durrani et al.[16]	0.0374	£141,538	£185,892	£275,797	£536,245	£7,411,362

*base case

In order to explore the impact of the cost of blindness, the AG undertook an analysis using the upper bounds of the 95% confidence intervals for the annual cost of blindness and the cost of the transition to blindness. Table 61 shows the result of these exploratory analyses, which result in lower ICERs of ADA

+ LCP(VII) versus LCP(VII) compared with the analyses using the mean blindness costs except when a blindness rate of 0 or a relative risk before treatment failure of 1 is assumed.

Table 61: ICERs of ADA + LCP(VII) versus LCP(VII) with varying blindness rates and RRs of blindness for patients before treatment using a high cost of blindness (upper bound of 95% CI)

		RR of blindness before treatment failure				
Source	**Rate**	**0 (no blindness)***	**0.25**	**0.50**	**0.75**	**1 (no effect)**
Assumption	0	£4,814,459	£4,814,459	£4,814,459	£4,814,459	£4,814,459
Tomkins-Netzer et al.[25]	0.0038	£523,933	£676,848	£953,341	£1,604,491	£4,988,973
Dick et al.[24]*	0.0066	£318,140*	£417,608	£604,860	£1,087,124	£5,133,625
Durrani et al.[16]	0.0374	£82,177	£109,245	£164,519	£327,767	£7,411,362

*base case

Exploratory analysis 3: Patients who go into remission due to adalimumab treatment

In the base case, the AG's model assumes that patients would stay on adalimumab until treatment failure. However, based on clinical advice received by the AG, a further analysis was undertaken which assumes that after two years of successful treatment, a proportion of patients would discontinue treatment and retain the benefits of treatment. Table 62 presents the results for different annual discontinuation rates for patients after two years of successful treatment. As expected, only the cost of treatment for the adalimumab varies with different rates of treatment discontinuation after remission: the cost of adalimumab treatment decreases as the rate of discontinuation increases and therefore the ICER for ADA + LCP(VII) versus LCP(VII) in patients with active uveitis decreases. It is worth noting that if all patients could discontinue adalimumab after two years and still retain the benefits of treatment, the ICER for ADA + LCP(VII) versus LCP(VII) is estimated to be £84,132 per QALY gained.

Table 62: ICERs of ADA + LCP(VII) versus LCP(VII) in patients with inactive uveitis assuming varying time to remission

Rate of remission		**Total QALYs**	**Total costs**	**Inc. QALYs**	**Inc. costs**	**ICER**
0*	LCP(VII)†	15.244	£48,111			
	ADA + LCP(VII)†	15.361	£85,462	0.116	£37,351	£321,405
0.10	LCP(VII)†	15.244	£48,111			
	ADA + LCP(VII)†	15.361	£71,241	0.116	£23,130	£199,031
0.25	LCP(VII)†	15.244	£48,111			
	ADA + LCP(VII)†	15.361	£64,710	0.116	£16,599	£142,832
1.00	LCP(VII)†	15.244	£48,111			
	ADA + LCP(VII)†	15.361	£57,888	0.116	£9,777	£84,132

*base case

†LCP(VII)= Limited current practice, as provided in the VISUAL II trial: on systemic steroids at baseline (10-35 mg/day) tapered by week 19 and around 47% of patients on systemic immunosuppressants.

Exploratory analysis 4: Using the VFQ-25 data from the VISUAL trials of adalimumab to map to EQ-5D utility data

The AG undertook an exploratory analysis using the VFQ-25 data from VISUAL II to map to EQ-5D instead of using directly measured EQ-5D. This analysis resulted in lower QALY gains and therefore in a higher ICER for ADA + LCP(VII) versus LCP(VII) compared with the base case (see Table 63).

Table 63: Results of ADA + LCP(VII) versus LCP(VII) in patients with inactive uveitis using EQ-5D scores captured in VISUAL II

	Total QALYs	**Total costs**	**Inc. QALYs**	**Inc. costs**	**ICER**
LCP(VII)*	15.100	£48,111			
ADA + LCP(VII)*	15.207	£85,462	0.107	£37,351	£348,094

*LCP(VII)= Limited current practice, as provided in the VISUAL II trial: on systemic steroids at baseline (10-35 mg/day) tapered by week 19 and around 47% of patients on systemic immunosuppressants.

Exploratory analysis 5: Extrapolation of time to treatment discontinuation for adalimumab

In order to assess the impact of the uncertainty on the extrapolation of the time to treatment failure, the AG undertook exploratory analyses using alternative parametric curves. The ICER for ADA + LCP(VII) versus LCP(VII) was lower when using a Gompertz distribution (£297,746 per QALY) or a Weibull distribution (£235,916 per QALY) compared with the log normal distribution used in the base case (£321,405 per QALY) (see Table 64).

Table 64: Results of ADA + LCP(VII) versus LCP(VII) in patients with inactive uveitis using different parametric curves to extrapolate time to treatment failure

Rate of remission		Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER
Log normal*	LCP(VII)†	15.244	£48,111			
	ADA + LCP(VII)†	15.361	£85,462	0.116	£37,351	£321,405
Gompertz	LCP(VII)†	15.305	£48,101			
	ADA + LCP(VII)†	15.628	£144,266	0.323	£96,166	£297,746
Weibull	LCP(VII)†	15.225	£48,114			
	ADA + LCP(VII)†	15.325	£71,577	0.099	£23,463	£235,916

*basecase

†LCP(VII)= Limited current practice, as provided in the VISUAL II trial: on systemic steroids at baseline (10-35 mg/day) tapered by week 19 and around 47% of patients on systemic immunosuppressants.

Univariate sensitivity analyses

The AG explored the impact of different parameters on the results of the model as shown in Table 65

The parameters which had a greatest impact on the ICER for ADA + LCP(VII) versus LCP(VII) were the baseline utility and the utility of blindness.

Table 65: Univariate sensitivity analyses for ADA + LCP(VII) versus LCP(VII) in patients with inactive uveitis. Base case ICER: £321,405 (deterministic)

Parameters	Base case, lower value, upper value	Lower value	Upper value
Utilities			
Baseline utility	[redacted], [redacted], [redacted]	£334,704	£309,733
Blindness utility	0.38, 0.31, 0.57	£279,904	£514,958
Administration and monitoring			
Monitoring visit frequency	6 weeks, 4 weeks, 8 weeks	£322,313	£320,952
Monitoring visit cost	£96.11, £77.27, £114.95	£320,956	£321,900
Adalimumab administration cost (help from a nurse)	£44, £35.80, £53.03	£320,628	£322,262
% of self-injectors needing district nurse for adalimumab	10%, 0%, 20%	£317,234	£325,577
AE costs			
Cataract surgery	£852.40, £658.33, £1019.47	£321,741	£321,035
Glaucoma procedure	£581.25, £467.32, £695.17	£321,405	£321,405
Serious infections	£5,940, £4,776, £7,105	£321,620	£321,169
Hypertension	£7.04, £5.66, £8.42	£321,405	£321,406
Blindness (transition)	£237, £191, £283	£321,409	£321,402
Blindness (annual)	£7,659, £6,158, £9,160	£324,667	£318,144

As for patients with active disease, of those parameters tested within the univariate sensitivity analysis, the parameters relating to the baseline utility and the utility of blindness had the greatest impact on the ICER for ADA + LCP(VII) versus LCP(VII). However, the ICER for adalimumab compared with current practice in patients with inactive uveitis does not fall below £84,000 per QALY gained in any of the analyses considered.

6.2.3 Discussion

Model results and key uncertainties

The base case analysis undertaken by the AG estimated the ICER of one dexamethasone implant in one eye for a combination of patients with unilateral and bilateral uveitis compared with limited current practice as per the HURON trial,[7] to be £19,509 per QALY gained. The ICER of adalimumab (systemic, therefore treatment for both eyes) for patients with mainly bilateral uveitis compared with limited current practice as per the VISUAL trials,[4, 5] is estimated to be £94,523 and £317,547 per QALY gained in patients with active and inactive uveitis respectively.

The results of the model are highly uncertain due to the limited availability of evidence. There are three major issues with the existing evidence: (1) there is no evidence comparing dexamethasone or adalimumab with current practice; (2) long term outcomes, in particular the incidence of permanent blindness, are uncertain; and (3) there is no evidence around the proportion of patients who would experience remission and be taken off adalimumab (or alternative) treatment or around long term

outcomes for these patients. These are structural uncertainties within the model and the complexity of these issues in combination with the lack of data meant that it was not possible to appropriately quantify the uncertainty associated with them within the probabilistic sensitivity analysis, as would be ideal. Instead, the potential impacts upon the model results of these factors have been dealt with using exploratory analysis.

These analyses suggest that the rate of blindness in the comparator group and the relative risk of blindness for dexamethasone and adalimumab substantially impact upon the ICER. The cost per QALY gained compared with the comparators within the trials ranged from dominating to £56,329 for dexamethasone. Under all assumptions tested for these parameters, the ICER associated with adalimumab compared with (limited) current practice remains above £30,000 and £82,000 for patients with active and inactive uveitis respectively. The choice of comparator did not substantially impact upon the ICER, though it should be noted that the rate of blindness was assumed to be the same for all comparators independent of the proportion of patients receiving systemic treatment, which may have slightly overestimated the QALYs associated with the placebo and sham groups and hence the ICERs for these comparisons may be slightly overestimated. The exploratory analyses also suggest show that the proportion of patients who would be taken off adalimumab treatment following remission and maintain the same quality of life is a key driver of the model results. Under the assumption that all patients who remain on adalimumab at two years achieve remission and are taken off treatment whilst retaining quality of life, the ICER for adalimumab compared with (limited) current practice decreases to £35,299 and £84,132 per QALY for patients with active and inactive uveitis respectively.

Use of adalimumab and dexamethasone in clinical practice

The clinical advisors to the AG suggest that there are several differences between the way in which the treatments are provided within the RCTs and the way in which they would be provided in practice. The clinical experts suggested that the proportion of patients who remain on adalimumab treatment is likely to be underestimated within the clinical trial because of the strict criteria for treatment failure. If more people were to remain on treatment, the additional group of patients on treatment would incur the same costs as those who remain on treatment in the VISUAL trial, whilst the effectiveness of adalimumab is likely to be reduced in these patients who were considered to have failed treatment in the trial, hence, the ICER would increase for these patients.

The model predicts that adalimumab would have a substantially higher ICER for inactive patients than active patients. VISUAL II captures the benefit of adalimumab over placebo for preventing recurrence of uveitis symptoms in patients who were inactive whilst on high dose steroids, once the steroids have been tapered and discontinued.[4, 5] However, our clinical advisors suggest that for the 'inactive' group of patients, adalimumab is more likely to be used in patients who have to discontinue existing

immunosuppressants because they are ineffective or not tolerated. However, there is no clinical data for this group of patients.

The model assumes that only one dexamethasone implant would be provided to patients. There is no RCT evidence to assess the comparative effectiveness or safety of more than one dexamethasone implant. However, there are several non-randomised trials with 12–24 months follow up, which allow repeat implants.[22, 48, 49] These studies consistently report that after around six months patients' outcomes return to those at baseline; and that up to three repeat implants are each likely to have a similar treatment effect. Each additional implant is associated with a higher incidence of adverse events such as IOP and cataract.[22, 48, 49] The univariate sensitivity analyses suggest that the model is not sensitive to the cost of IOP or cataract, and hence, given that the cost of each implant is the same, the cost-effectiveness of up to three consecutive implants is expected to be similar to the cost-effectiveness of one implant. The ICER would be expected to decrease if there was also a cumulative impact upon the reduction in blindness or if patients were to achieve remission after consecutive implants. The clinical experts to the AG suggested that the maximum number of implants they are likely to provide to one eye per patient is four because of the increasing rates of IOP for each implant. Clinicians suggested that the increasing rate of cataract would not affect their decision regarding additional implants because the condition is reversible with surgery.

Clinical advice suggests that patients would not usually have an implant in both eyes because they are more likely to have a systemic treatment if both eyes require improvement; however, this may occur in some cases. There is insufficient evidence to assess the cost-effectiveness of using dexamethasone implants in both eyes; however, because the costs would essentially be doubled (with the exception of some monitoring costs) and the increment in HRQoL is likely to be lower for the second eye, it is expected to be less cost-effective than treatment in one eye for a patient with bilateral disease.

The clinicians to the AG suggest that adalimumab and dexamethasone are likely to be provided alongside other treatment options in practice. In the clinical trials, around a third of patients did receive other treatments in both arms. However, it is unclear whether the relative effectiveness of adalimumab and dexamethasone predicted within the trials would remain if alternative treatment in both the intervention and comparator groups were increased. If the relative effectiveness and costs remained the same, then the ICER would not change from the base case predicted ICER.

However, due to the lack of evidence for a comparator which represents current practice, it is unclear how both adalimumab and dexamethasone may impact upon the use of other treatments. The model incorporates the impact of dexamethasone upon rescue therapy, but this is based upon the analysis using a sham comparator. If dexamethasone or adalimumab led to a reduction in the use of immunosuppressants and/or corticosteroids without this impacting upon efficacy in these treatment groups, then they would be more cost-effective than currently predicted.

Potentially important subgroups

The model is made up of a heterogeneous population, and it may be that the interventions are more cost-effectiveness in some groups than others. However, there is insufficient evidence to undertake any formal subgroup analyses. This discussion considers the key subgroups for which the interventions may be more cost-effective. Almost all patients receiving adalimumab will have bilateral uveitis; however dexamethasone may also be given to patients with unilateral uveitis. Dexamethasone is likely to be more cost-effective when given in one eye to patients with bilateral uveitis because BCVA in the better-seeing eye is the best predictor of quality of life and hence bilateral uveitis patients are generally able to benefit more from treatment than unilateral uveitis patients, at the same cost of treatment. Where the annual rate of blindness is set to 0, the results could be used to give an indication around the cost-effectiveness of dexamethasone for patients with unilateral disease (since patients with unilateral disease are unlikely to become legally blind, unless their disease progresses to become bilateral). This results in an ICER of £48,937. It is important to note that the treatment effect may also be different (expected to be reduced) for unilateral patients compared with a pooled group of unilateral and bilateral patients; however there is no evidence available to model this.

Patients also have the potential to benefit more from treatment with adalimumab or dexamethasone if they have more severe uveitis, and hence the treatments are likely to be more cost-effective as the baseline disease worsens. In addition, patients with macular oedema would be more likely to go blind and hence the interventions of interest, in particular adalimumab due to the longer duration of treatment, are more likely to prevent cases of blindness and hence are likely to be more cost-effective in this group.

Model perspective

Currently, the base case analysis takes an NHS and PSS perspective. However, non-infectious uveitis affects a working-age population and can reduce workplace productivity. In addition, the disease can affect leisure time. Therefore, there are likely to be additional non NHS and PSS costs and benefits of the interventions not captured within our analyses.

7 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

Many uveitis treatments used in clinical practice are not licensed for uveitis, and injections of triamcinolone are contraindicated in the eye (Kenalog formation) or not available in the UK (Trivaris/Triesence formulation). Dexamethasone implants and adalimumab are both used variably in current practice, depending on funding availability. Posterior segment-involving uveitis covers a broad spectrum of patients. Dexamethasone implants and adalimumab would generally be used in different populations in clinical practice (dexamethasone for local disease or local flare-up and in unilateral cases; adalimumab for severe refractory disease, often bilateral and/or related to a systemic condition). There is little trial data relating to patients who have very severe uveitis or who are unresponsive to or contraindicated for immunosuppressants.

Prevalence is estimated to be between 3 and 10 in 100,000 people in the European Union based upon a population of 506,500,000, including people from the UK.[124] The mid-2015 estimate for the adult population of England is 43,108,471.[125] This results in an estimated prevalence of non-infectious posterior segment involving uveitis in adults in England of between 1293 and 4311. Within their submission to NICE, Allergan, however, estimate a higher prevalence of 16.14 per 100,000 based upon a US study, which would result in a higher estimate of 6,958 adults affected by non-infectious posterior segment uveitis in England. In their submission, Abbvie predict that 5,389 adults would be affected by non-infectious posterior segment uveitis in England. The proportion of patients that would receive dexamethasone and adalimumab within this patient group is highly uncertain. Within their submission to NICE, Allergan predict that 589 patients would be eligible for dexamethasone annually (8.0% of the Allergan predicted number of patients with non-infectious posterior segment uveitis), whilst Abbvie predict that 175 patients would be eligible for adalimumab annually (3.2% of the Abbvie predicted patients with non-infectious posterior segment uveitis).

Provision of adalimumab and dexamethasone does not usually engender significant additional management costs compared with current practice. Therefore, the burden upon the NHS is generally in terms of the additional drug acquisition costs and differences in the treatment of adverse events.

8 DISCUSSION

8.1 Statement of principle findings

One RCT of adalimumab in patients with active uveitis (VISUAL I[4, 5], n=223, up to 80 weeks) showed significant benefits over placebo for time to treatment failure as well as visual acuity, inflammation (VH and AC cell grade), macular oedema (change in central retinal thickness) and the VFQ-25. Another RCT of adalimumab in patients with inactive uveitis controlled with corticosteroids (VISUAL II[4, 5], n=229, up to 80 weeks) showed significant benefit over placebo for time to treatment failure but not for the other outcomes. There were some concerns regarding use of LOCF to account for missing data after patients experienced treatment failure in the ADA studies, since these data were not missing at random. The base case analysis undertaken by the AG estimated the ICER of one dexamethasone implant in one eye for a combination of patients with unilateral and bilateral uveitis compared with limited current practice as per the HURON trial,[7] to be £19,509 per QALY gained.

A 26-week study of dexamethasone implant 0.7mg (HURON, n=153 for relevant groups) showed significant improvements over sham for measures of visual acuity, inflammation (VH and AC cells), macular oedema (central retinal thickness) and VFQ-25. The ICER of adalimumab (systemic, therefore treatment for both eyes) for patients with mainly bilateral uveitis compared with limited current practice as per the VISUAL trials,[4, 5] is estimated to be £94,523 and £317,547 per QALY gained in patients with active and inactive uveitis respectively.

Exploratory analyses suggest that two of the factors with the largest impact upon the ICERs, both of which are highly uncertain, are the rate of blindness in the comparator group and the relative risk of blindness for adalimumab and dexamethasone. The incremental cost-effectiveness for dexamethasone compared with (limited) current practice varies from dominating to an ICER of £56,329 per QALY gained under different assumptions for these parameters. Where the rate of legal blindness is set to zero, this is used to explore the potential cost-effectiveness of dexamethasone for patients with unilateral uveitis, which has an estimated ICER of £50,627. Under all assumptions tested for these parameters, the ICER associated with adalimumab compared with (limited) current practice remains above £30,000 and £82,000 for patients with active and inactive uveitis respectively. The proportion of patients taken off adalimumab treatment following remission and maintaining the same quality of life has the largest impact upon the ICER for adalimumab, reducing it to £35,299 and £84,132 per QALY for patients with active and inactive uveitis respectively when assuming all patients go on remission after two years on adalimumab.

8.2 Strengths and limitations of the assessment

We have attempted to compare the two interventions being assessed with current practice. However, we have no RCT evidence which compares any two treatments within the scope of the assessment. Adalimumab was compared to placebo in both studies (patients in both arms received initial systemic corticosteroids which were then tapered, and some also received an immunosuppressant). Dexamethasone was compared to sham procedure (25% continued a stable dose of systemic corticosteroids or immunosuppressants, and rescue therapy, either local steroid injection or new/increased systemic therapy, was received by 22% in both the DEX 700 and sham arms. The placebo/sham arms could be considered to represent standard practice to some extent because other therapies were permitted in both the active treatment and placebo arms in all three studies. However, the main comparison was to placebo/sham as opposed to active management with other therapies.

It was not possible to conduct meta-analyses or network meta-analyses because of clinical heterogeneity, lack of common comparators (disconnected network) and differences in reported outcomes.

The health economic model is the first model which has attempted to assess the cost-effectiveness of adalimumab or dexamethasone for the treatment of non-infectious uveitis. However, the results are highly uncertain due to the limited availability of evidence and the differences between the trial evidence and clinical practice (as discussed within Section 6.2).

The model is made up of a heterogeneous population, and it may be that the interventions are more cost-effectiveness in some groups than others. However, there is no evidence from the trials to undertake subgroup analyses. Patients have the potential to benefit more from treatment with adalimumab or dexamethasone if they have more severe uveitis, and hence the treatments are likely to be more cost-effective as the baseline disease worsens. In addition, patients with macular oedema would be more likely to go blind and hence the interventions of interest, in particular adalimumab due to the longer duration of treatment, are more likely to prevent cases of blindness and hence are likely to be more cost-effective in this group. The exploratory analysis varying the rate of blindness to represent patients with unilateral uveitis suggests that the ICER for dexamethasone compared with (limited) current practice increases substantially for this patient group; however the treatment effect for the subgroup is assumed to remain unchanged.

The analysis presented here takes an NHS and PSS perspective. However, non-infectious uveitis affects a working-age population and can reduce workplace productivity. In addition, the disease can affect leisure time. Therefore, there are likely to be additional non NHS and PSS costs and benefits of the interventions not captured within our analyses.

8.3 Uncertainties

The key uncertainties associated with this evaluation are:

- The comparative effectiveness and cost-effectiveness of dexamethasone and adalimumab with each other and with systemic immunosuppressants and corticosteroids as would be used in practice;
- How short-term improvements in visual acuity and inflammation relate to long-term effects on vision loss and blindness;
- The way in which adalimumab and dexamethasone would be used in practice, particularly regarding taking patients off treatment following remission and the number of dexamethasone implants that would be provided;
- The impact of the expected differences between clinical practice and the trial evidence upon estimated outcomes;
- The effectiveness and cost-effectiveness of adalimumab and dexamethasone in subgroups, including patients with unilateral and bilateral uveitis, those with more and less severe uveitis, patients who are unresponsive to or contraindicated for immunosuppressants, patients with macular oedema, and patients with underlying autoimmune or inflammatory diseases;
- The long term impacts of corticosteroids.

8.4 Other relevant factors

The number of patients that would be eligible for these treatments is low. Dexamethasone implants and adalimumab are currently generally used in very different patient populations in clinical practice.

9 CONCLUSIONS

Two RCTs of adalimumab and one of dexamethasone implant showed significant benefits over placebo or sham on outcomes including visual acuity, inflammation (VH and AC cells), macular oedema (central retinal thickness), the visual function questionnaire (VFQ-25), and time to treatment failure. One dexamethasone implant in a mixed group of unilateral and bilateral patients has an estimated ICER of £19,509 per QALY gained compared with (limited) current practice. The ICER associated with adalimumab compared with (limited) current practice, does not fall below £30,000 per QALY gained for any analyses tested.

There is substantial uncertainty around the evidence, in particular the comparative effectiveness and cost-effectiveness of dexamethasone and adalimumab with each other and with systemic immunosuppressants and corticosteroids as would be used in practice, and how short-term improvements in visual acuity and inflammation relate to long-term effects on vision loss and blindness. In addition, the way in which adalimumab and dexamethasone would be used in practice and the impact of the expected differences between clinical practice and the trial evidence upon estimated outcomes is uncertain. Finally, there are important subgroups for which the interventions may be more or less effective and cost-effective; however there is insufficient evidence to make robust conclusions around these.

9.1 Implications for service provision

Provision of adalimumab and dexamethasone does not usually engender significant additional management costs. Therefore, the burden upon the NHS is generally in terms of the drug acquisition costs and treatment of adverse events.

9.2 Suggested research priorities

- Primary research comparing the use of dexamethasone and adalimumab with immunosuppressants or other anti-TNFs over the long term.
- Research on how short-term improvements in visual acuity or inflammation relate to long-term effects on moderate to severe vision loss and blindness.
- An assessment of the impact of treatments within important subgroups, including patients with unilateral and bilateral uveitis, those with severe uveitis, patients who are unresponsive to or contraindicated for immunosuppressants, patients with macular oedema, and patients with underlying autoimmune or inflammatory diseases.
- A study of the long term impacts of corticosteroids to gain further data on the health and utility detriments and costs.

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11 APPENDICES

Appendix 1: Literature Search Strategies

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
13th June 2016

#	Searches
1	exp Uveitis/
2	uveiti*.mp.
3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*).tw.
4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*).tw.
5	((vogt or harada or behcet* or blau* or jabs or reiter*) adj (disease or syndrome)).tw.
6	(vogt koyanagi harada or triple symptom complex).tw.
7	(ophthalm* adj2 sympathetic).tw.
8	exp Retinitis/
9	(retinitis or vitritis* or uveoretinitis or neuroretinitis).tw.
10	or/1-9
11	Meta-Analysis as Topic/
12	meta analy$.tw.
13	metaanaly$.tw.
14	Meta-Analysis/
15	(systematic adj (review$1 or overview$1)).tw.
16	exp Review Literature as Topic/
17	or/11-16
18	cochrane.ab.
19	embase.ab.
20	(psychlit or psyclit).ab.
21	(psychinfo or psycinfo).ab.
22	(cinahl or cinhal).ab.
23	science citation index.ab.
24	bids.ab.
25	cancerlit.ab.
26	or/18-25
27	reference list$.ab.
28	bibliograph$.ab.
29	hand-search$.ab.
30	relevant journals.ab.
31	manual search$.ab.
32	or/27-31
33	selection criteria.ab.
34	data extraction.ab.
35	33 or 34
36	Review/
37	35 and 36

38	Comment/
39	Letter/
40	Editorial/
41	animal/
42	human/
43	41 not (41 and 42)
44	or/38-40,43
45	17 or 26 or 32 or 37
46	45 not 44
47	Randomized Controlled Trials as Topic/
48	randomized controlled trial/
49	Random Allocation/
50	Double Blind Method/
51	Single Blind Method/
52	clinical trial/
53	clinical trial, phase i.pt.
54	clinical trial, phase ii.pt.
55	clinical trial, phase iii.pt.
56	clinical trial, phase iv.pt.
57	controlled clinical trial.pt.
58	randomized controlled trial.pt.
59	multicenter study.pt.
60	clinical trial.pt.
61	exp Clinical Trials as topic/
62	or/47-61
63	(clinical adj trial$).tw.
64	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
65	PLACEBOS/
66	placebo$.tw.
67	randomly allocated.tw.
68	(allocated adj2 random$).tw.
69	or/63-68
70	62 or 69
71	case report.tw.
72	letter/
73	historical article/
74	or/71-73
75	70 not 74
76	10 and (46 or 75)

Embase 1974 to 2016 June 10
13th June 2016

#	**Searches**
1	exp uveitis/
2	uveiti*.mp.
3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*).tw.

4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*).tw.
5	((vogt or harada or behcet* or blau* or jabs or reiter*) adj (disease or syndrome)).tw.
6	(vogt koyanagi harada or triple symptom complex).tw.
7	(ophthalm* adj2 sympathetic).tw.
8	exp retinitis/
9	(retinitis or vitritis* or uveoretinitis or neuroretinitis).tw.
10	or/1-9
11	exp Meta Analysis/
12	((meta adj analy$) or metaanalys$).tw.
13	(systematic adj (review$1 or overview$1)).tw.
14	or/11-13
15	cancerlit.ab.
16	cochrane.ab.
17	embase.ab.
18	(psychlit or psyclit).ab.
19	(psychinfo or psycinfo).ab.
20	(cinahl or cinhal).ab.
21	science citation index.ab.
22	bids.ab.
23	or/15-22
24	reference lists.ab.
25	bibliograph$.ab.
26	hand-search$.ab.
27	manual search$.ab.
28	relevant journals.ab.
29	or/24-28
30	data extraction.ab.
31	selection criteria.ab.
32	30 or 31
33	review.pt.
34	32 and 33
35	letter.pt.
36	editorial.pt.
37	animal/
38	human/
39	37 not (37 and 38)
40	or/35-36,39
41	14 or 23 or 29 or 34
42	41 not 40
43	Clinical trial/
44	Randomized controlled trial/
45	Randomization/
46	Single blind procedure/
47	Double blind procedure/
48	Crossover procedure/

49	Placebo/
50	Randomi?ed controlled trial$.tw.
51	Rct.tw.
52	Random allocation.tw.
53	Randomly allocated.tw.
54	Allocated randomly.tw.
55	(allocated adj2 random).tw.
56	Single blind$.tw.
57	Double blind$.tw.
58	((treble or triple) adj blind$).tw.
59	Placebo$.tw.
60	Prospective study/
61	or/43-60
62	Case study/
63	Case report.tw.
64	Abstract report/ or letter/
65	or/62-64
66	61 not 65
67	10 and (42 or 66)

Web of Science® Core Collection
Science Citation Index Expanded (1900-)
Conference Proceedings Citation Index - Science (1990-)
13th June 2016

#	Searches
# 1	TOPIC: (uveiti*)
# 2	TOPIC: ((panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*))
# 3	TOPIC: ((iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*))
# 4	TOPIC: (((vogt or harada or behcet* or blau* or jabs or reiter*) near (disease or syndrome)))
# 5	TOPIC: ((vogt koyanagi harada or triple symptom complex))
# 6	TOPIC: ((ophthalm* near/2 sympathetic))
# 7	TOPIC: ((retinitis or vitritis* or uveoretinitis or neuroretinitis))
# 8	#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
# 9	TOPIC: (("clinic* trial*" or "randomi* controlled trial*")) OR TOPIC: (((singl* or doubl* or treb* or tripl*) and (blind* or mask*))) OR TOPIC: ((placebo*)) OR TOPIC: ((allocat* and random*))
#10	TOPIC: ((meta-analysis or meta analy* or metaanaly*)) OR TOPIC: (("review literature" or "literature review")) OR TOPIC: (("systematic review*" or "systematic overview*")) OR TOPIC: ((cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit)) OR TOPIC: (("reference list*" or bibliograph* or hand-search* or "relevant journals" or "manual search*")) OR TOPIC: ((("selection criteria" or "data extraction") and review))
#11	#10 OR #9
#12	#11 AND #8

Cochrane Database of Systematic Reviews (CDR): Wiley Online.

Cochrane Central Register of Controlled Trials (CENTRAL): Wiley Online.
Health Technology Assessment Database (HTA): Wiley Online.
Database of Abstracts of Reviews of Effects (DARE)): Wiley Online. 1995-2015
NHS Economic Evaluation Database (NHS EED): Wiley Online. 1995-2015
13th June 2016

#	Searches
#1	MeSH descriptor: [Uveitis] explode all trees
#2	uveiti*:ti,ab,kw
#3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*):ti,ab,kw
#4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*):ti,ab,kw
#5	((vogt or harada or behcet* or blau* or jabs or reiter*) near (disease or syndrome)):ti,ab,kw
#6	(vogt koyanagi harada or triple symptom complex):ti,ab,kw
#7	(ophthalm* near/2 sympathetic):ti,ab,kw
#8	MeSH descriptor: [Retinitis] explode all trees
#9	(retinitis or vitritis* or uveoretinitis or neuroretinitis):ti,ab,kw
#10	#1 or #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

CINAHL 1982 to Present
6th October 2016

#	Searches
S1	(MH "Uveitis+")
S2	uveiti*
S3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*)
S4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*)
S5	((vogt or harada or behcet* or blau* or jabs or reiter*) N1 (disease or syndrome))
S6	(vogt koyanagi harada or triple symptom complex)
S7	(ophthalm* N2 sympathetic)
S8	(MH "Retinitis+")
S9	(retinitis or vitritis* or uveoretinitis or neuroretinitis)
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
S11	(MH "Meta Analysis")
S12	TI ((Meta analys* or Metaanaly*)) or AB ((Meta analys* or Metaanaly*))
S13	(MH "Literature Review+")
S14	systematic N2 review or systematic N2 overview
S15	S11 or S12 or S13 or S14
S16	PT Commentary or PT Letter or PT Editorial
S17	(MH "Animals")
S18	S16 or S17
S19	S15 not S18
S20	(MH "Clinical Trials+")
S21	PT Clinical trial
S22	TI Randomi?ed control* trial* or AB Randomi?ed control* trial*
S23	(MH "Random Assignment")

S24	(MH "Quantitative Studies")
S25	TI Allocat* random* or AB Allocat* random*
S26	TI Random* allocat* or AB Random* allocat*
S27	TI Placebo* or AB Placebo*
S28	TI Placebos or AB Placebos
S29	TI ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)) or AB ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*))
S30	TI clinic* N1 trial* or AB clinic* N1 trial*
S31	S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30
S32	S10 and (S19 or S31)

Cost-effectiveness studies

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
6 June 2016

#	Searches
1	exp Uveitis/
2	uveiti*.mp.
3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*).tw.
4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*).tw.
5	((vogt or harada or behcet* or blau* or jabs or reiter*) adj (disease or syndrome)).tw.
6	(vogt koyanagi harada or triple symptom complex).tw.
7	(ophthalm* adj2 sympathetic).tw.
8	exp Retinitis/
9	(retinitis or vitritis* or uveoretinitis or neuroretinitis).tw.
10	or/1-9
11	Economics/
12	"costs and cost analysis"/
13	Cost-benefit analysis/
14	Cost control/
15	Cost savings/
16	Cost of illness/
17	Cost sharing/
18	"deductibles and coinsurance"/
19	Medical savings accounts/
20	Health care costs/
21	Direct service costs/
22	Drug costs/
23	Employer health costs/
24	Hospital costs/
25	Health expenditures/
26	Capital expenditures/
27	Value of life/
28	exp economics, hospital/
29	exp economics, medical/
30	Economics, nursing/
31	Economics, pharmaceutical/
32	exp "fees and charges"/
33	exp budgets/

34	(low adj cost).mp.
35	(high adj cost).mp.
36	(health?care adj cost*).mp.
37	(fiscal or funding or financial or finance).tw.
38	(cost adj estimate*).mp.
39	(cost adj variable).mp.
40	(unit adj cost*).mp.
41	(economic* or pharmacoeconomic* or price* or pricing).tw.
42	or/11-41
43	10 and 42

Embase 1974 to 2016 June 03
7 June 2016

#	Searches
1	exp uveitis/
2	uveiti*.mp.
3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*).tw.
4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*).tw.
5	((vogt or harada or behcet* or blau* or jabs or reiter*) adj (disease or syndrome)).tw.
6	(vogt koyanagi harada or triple symptom complex).tw.
7	(ophthalm* adj2 sympathetic).tw.
8	exp retinitis/
9	(retinitis or vitritis* or uveoretinitis or neuroretinitis).tw.
10	or/1-9
11	Socioeconomics/
12	Cost benefit analysis/
13	Cost effectiveness analysis/
14	Cost of illness/
15	Cost control/
16	Economic aspect/
17	Financial management/
18	Health care cost/
19	Health care financing/
20	Health economics/
21	Hospital cost/
22	(fiscal or financial or finance or funding).tw.
23	Cost minimization analysis/
24	(cost adj estimate*).mp.
25	(cost adj variable*).mp.
26	(unit adj cost*).mp.
27	or/11-26
28	10 and 27

Web of Science® Core Collection
Science Citation Index Expanded (1900-)
Conference Proceedings Citation Index - Science (1990-)
7 June 2016

#	Searches
# 1	**TOPIC:** (uveiti*)
# 2	**TOPIC:** ((panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*))

# 3	**TOPIC:** ((iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*))
# 4	**TOPIC:** (((vogt or harada or behcet* or blau* or jabs or reiter*) near (disease or syndrome)))
# 5	**TOPIC:** ((vogt koyanagi harada or triple symptom complex))
# 6	**TOPIC:** ((ophthalm* near/2 sympathetic))
# 7	**TOPIC:** ((retinitis or vitritis* or uveoretinitis or neuroretinitis))
# 8	#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
# 9	**TOPIC:** ((cost* and (effective* or utilit* or benefit* or minimi*))) *OR* **TOPIC:** (cost*) *OR* **TOPIC:** ((economic* or pharmacoeconomic* or pharmaco-economic*)) *OR* **TOPIC:** ((financial or finance or finances or financed)) *OR* **TOPIC:** ((fee or fees)) *OR* **TOPIC:** ((value and (money or monetary))) *OR* **TOPIC:** ((economic* and (hospital or medical or nursing or pharmaceutical))) *OR* **TOPIC:** (("quality adjusted life year" or "quality adjusted life years")) *OR* **TOPIC:** ((qaly or qalys)) *OR* **TOPIC:** (budget*) *OR* **TOPIC:** ((price* or pricing*))
# 10	#9 AND #8

Cochrane Database of Systematic Reviews (CDR): Wiley Online.
Health Technology Assessment Database (HTA): Wiley Online.
NHS Economic Evaluation Database (NHS EED): Wiley Online. 1995-2015
7 June 2016

#	Searches
#1	MeSH descriptor: [Uveitis] explode all trees
#2	uveiti*:ti,ab,kw
#3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*):ti,ab,kw
#4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*):ti,ab,kw
#5	((vogt or harada or behcet* or blau* or jabs or reiter*) near (disease or syndrome)):ti,ab,kw
#6	(vogt koyanagi harada or triple symptom complex):ti,ab,kw
#7	(ophthalm* near/2 sympathetic):ti,ab,kw
#8	MeSH descriptor: [Retinitis] explode all trees
#9	(retinitis or vitritis* or uveoretinitis or neuroretinitis):ti,ab,kw
#10	#1 or #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

CINAHL 1982 to Present
6th October 2016

#	Searches
S1	(MH "Uveitis+")
S2	uveiti*
S3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*)
S4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*)
S5	((vogt or harada or behcet* or blau* or jabs or reiter*) N1 (disease or syndrome))
S6	(vogt koyanagi harada or triple symptom complex)
S7	(ophthalm* N2 sympathetic)
S8	(MH "Retinitis+")
S9	(retinitis or vitritis* or uveoretinitis or neuroretinitis)
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
S11	(MH "Costs and Cost Analysis+")

S12	(MH "Economics")
S13	(MH "Economics, Pharmaceutical")
S14	(MH "Fees and Charges+")
S15	(MH "Budgets")
S16	budget*
S17	cost*
S18	AB cost* and (effective* or utilit* or benefit* or minimi*)
S19	TI economic* or pharmacoeconomic* or pharmaco-economic*
S20	price* or pricing*
S21	financial or finance or finances or financed
S22	fee or fees
S23	value and (money or monetary)
S24	qaly or qalys
S25	quality adjusted life year or quality adjusted life years
S26	S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25
S27	S10 AND S26

Quality of life studies

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
9 June 2016

#	Searches
1	exp Uveitis/
2	uveiti*.mp.
3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*).tw.
4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*).tw.
5	((vogt or harada or behcet* or blau* or jabs or reiter*) adj (disease or syndrome)).tw.
6	(vogt koyanagi harada or triple symptom complex).tw.
7	(ophthalm* adj2 sympathetic).tw.
8	exp Retinitis/
9	(retinitis or vitritis* or uveoretinitis or neuroretinitis).tw.
10	or/1-9
11	"Quality of Life"/
12	(qol or (quality adj2 life)).ab,ti.
13	(value adj2 (money or monetary)).tw.
14	value of life/
15	quality adjusted life year/
16	quality adjusted life.tw.
17	(qaly* or qald* or qale* or qtime*).tw.
18	disability adjusted life.tw.
19	daly*.tw.
20	health status indicators/
21	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
22	(sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

23	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
24	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.
25	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
26	(euroqol or euro qol or eq5d or eq 5d).tw.
27	(hql or hqol or h qol or hrqol or hr qol).tw.
28	(hye or hyes).tw.
29	health* year* equivalent*.tw.
30	health utilit*.tw.
31	(hui or hui1 or hui2 or hui3).tw.
32	disutilit*.tw.
33	rosser.tw.
34	(quality adj2 wellbeing).tw.
35	qwb.tw.
36	(willingness adj2 pay).tw.
37	standard gamble*.tw.
38	time trade off.tw.
39	time tradeoff.tw.
40	tto.tw.
41	letter.pt.
42	editorial.pt.
43	comment.pt.
44	41 or 42 or 43
45	or/11-40
46	45 not 44
47	10 and 46

Embase 1974 to 2016 June 08
9 June 2016

#	Searches
1	exp uveitis/
2	uveiti*.mp.
3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*).tw.
4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*).tw.
5	((vogt or harada or behcet* or blau* or jabs or reiter*) adj (disease or syndrome)).tw.
6	(vogt koyanagi harada or triple symptom complex).tw.
7	(ophthalm* adj2 sympathetic).tw.
8	exp retinitis/
9	(retinitis or vitritis* or uveoretinitis or neuroretinitis).tw.
10	or/1-9
11	"Quality of Life"/
12	(qol or (quality adj2 life)).ti,ab.
13	(value adj2 (money or monetary)).tw.
14	socioeconomics/
15	quality adjusted life year/
16	(qaly$ or qald$ or qale$ or qtime$).tw.
17	disability adjusted life.tw.
18	daly$.tw.
19	health survey/

20	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
21	(sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
22	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
23	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.
24	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
25	(euroqol or euro qol or eq5d or eq 5d).tw.
26	(hql or hqol or h qol or hrqol or hr qol).tw.
27	(hye or hyes).tw.
28	health$ year$ equivalent$.tw.
29	health utilit$.tw.
30	(hui or hui1 or hui2 or hui3).tw.
31	disutilit$.tw.
32	rosser.tw.
33	(quality adj2 wellbeing).tw.
34	qwb.tw.
35	(willingness adj2 pay).tw.
36	standard gamble$.tw.
37	time trade off.tw.
38	time tradeoff.tw.
39	tto.tw.
40	letter.pt.
41	editorial.pt.
42	comment.pt.
43	40 or 41 or 42
44	or/11-39
45	44 not 43
46	10 and 45

Web of Science® Core Collection
Science Citation Index Expanded (1900-)
Conference Proceedings Citation Index - Science (1990-)
9 June 2016

#	Searches
# 1	**TOPIC:** (uveiti*)
# 2	**TOPIC:** ((panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*))
# 3	**TOPIC:** ((iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*))
# 4	**TOPIC:** (((vogt or harada or behcet* or blau* or jabs or reiter*) near (disease or syndrome)))
# 5	**TOPIC:** ((vogt koyanagi harada or triple symptom complex))
# 6	**TOPIC:** ((ophthalm* near/2 sympathetic))
# 7	**TOPIC:** ((retinitis or vitritis* or uveoretinitis or neuroretinitis))
# 8	#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
# 9	**TOPIC:** ((qol or "quality of life" or "quality adjusted life")) *OR* **TOPIC:** ((qaly* or qald* or qale* or qtime*)) *OR* **TOPIC:** (("disability adjusted life" or daly*)) *OR* **TOPIC:** ((sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six)) *OR* **TOPIC:** ((sf 6

	or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six)) *OR* **TOPIC:** ((sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve)) *OR* **TOPIC:** ((sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen)) *OR* **TOPIC:** ((sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty)) *OR* **TOPIC:** ((euroqol or euro qol or eq5d or eq 5d)) *OR* **TOPIC:** ((hql or hqol or h qol or hrqol or hr qol)) *OR* **TOPIC:** ((hye or hyes)) *OR* **TOPIC:** (("health* year* equivalent*")) *OR* **TOPIC:** (("health utilit*")) *OR* **TOPIC:** ((hui or hui1 or hui2 or hui3)) *OR* **TOPIC:** ((disutilit* or rosser)) *OR* **TOPIC:** (("quality of wellbeing" or qwb or "willingness to pay")) *OR* **TOPIC:** (("standard gamble*" or "time trade off" or "time tradeoff" or tto))
#10	#9 AND #8

Cochrane Database of Systematic Reviews (CDR): Wiley Online.
Health Technology Assessment Database (HTA): Wiley Online.
NHS Economic Evaluation Database (NHS EED): Wiley Online. 1995-2015
9 June 2016

#	Searches
#1	MeSH descriptor: [Uveitis] explode all trees
#2	uveiti*:ti,ab,kw
#3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*):ti,ab,kw
#4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*):ti,ab,kw
#5	((vogt or harada or behcet* or blau* or jabs or reiter*) near (disease or syndrome)):ti,ab,kw
#6	(vogt koyanagi harada or triple symptom complex):ti,ab,kw
#7	(ophthalm* near/2 sympathetic):ti,ab,kw
#8	MeSH descriptor: [Retinitis] explode all trees
#9	(retinitis or vitritis* or uveoretinitis or neuroretinitis):ti,ab,kw
#10	#1 or #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

CINAHL 1982 to Present
6th October 2016

#	Searches
S1	(MH "Uveitis+")
S2	uveiti*
S3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*)
S4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*)
S5	((vogt or harada or behcet* or blau* or jabs or reiter*) N1 (disease or syndrome))
S6	(vogt koyanagi harada or triple symptom complex)
S7	(ophthalm* N2 sympathetic)
S8	(MH "Retinitis+")
S9	(retinitis or vitritis* or uveoretinitis or neuroretinitis)
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
S11	(MH "Quality of Life")
S12	TI (qol or (quality N2 life)) or AB (qol or (quality N2 life))
S13	TI value and TI (money or monetary) or AB value and AB (money or monetary)
S14	(MH "Economic Value of Life")
S15	(MH "Quality-Adjusted Life Years")

S16	TI (qaly* or qald* or qale* or qtime*) or AB (qaly* or qald* or qale* or qtime*)
S17	TI disability adjusted life or AB disability adjusted life
S18	TI daly* or AB daly*
S19	(MH "Health Status Indicators")
S20	TI (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six) or AB (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six)
S21	TI (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six) or AB (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six)
S22	TI quality adjusted life or AB quality adjusted life
S23	TI (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve) or AB (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve)
S24	TI (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen) or AB (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen)
S25	TI (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty) or AB (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty)
S26	TI (euroqol or euro qol or eq5d or eq 5d) or AB (euroqol or euro qol or eq5d or eq 5d)
S27	TI (hql or hqol or h qol or hrqol or hr qol) or AB (hql or hqol or h qol or hrqol or hr qol)
S28	TI (hye or hyes) or AB (hye or hyes)
S29	TI health* year* equivalent* or AB health* year* equivalent*
S30	TI health utilit* or AB health utilit*
S31	TI (hui or hui1 or hui2 or hui3) or AB (hui or hui1 or hui2 or hui3)
S32	TI disutilit* or AB disutilit*
S33	TI rosser or AB rosser
S34	TI quality N2 wellbeing or AB quality N2 wellbeing
S35	TI qwb or AB qwb
S36	TI willingness N2 pay or AB willingness N2 pay
S37	TI standard gamble* or AB standard gamble*
S38	TI time trade off or AB time trade off
S39	TI time tradeoff or AB time tradeoff
S40	TI tto or AB tto
S41	PT letter
S42	PT editorial
S43	PT comment
S44	S41 or S42 or S43
S45	S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40
S46	S45 NOT S44
S47	S10 AND S46

Costs and utilities of blindness

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

17th October 2016

#	Searches
1	blindness.ti.
2	((sight or visual or vision) adj1 loss).ti.
3	1 or 2
4	exp "costs and cost analysis"/
5	costs.tw.
6	cost effective:.tw.
7	or/4-6
8	3 and 7
9	limit 8 to yr="2006 -Current"
10	"Quality of Life"/
11	(qol or (quality adj2 life)).ab,ti.
12	(value adj2 (money or monetary)).tw.
13	value of life/
14	quality adjusted life year/
15	quality adjusted life.tw.
16	(qaly$ or qald$ or qale$ or qtime$).tw.
17	disability adjusted life.tw.
18	daly$.tw.
19	health status indicators/
20	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
21	(sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
22	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
23	(sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).tw.
24	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
25	(euroqol or euro qol or eq5d or eq 5d).tw.
26	(hql or hqol or h qol or hrqol or hr qol).tw.
27	(hye or hyes).tw.
28	health$ year$ equivalent$.tw.
29	health utilit$.tw.
30	(hui or hui1 or hui2 or hui3).tw.
31	disutilit$.tw.
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36	standard gamble$.tw.

37	time trade off.tw.
38	time tradeoff.tw.
39	tto.tw.
40	letter.pt.
41	editorial.pt.
42	comment.pt.
43	40 or 41 or 42
44	or/10-39
45	44 not 43
46	3 and 45

Appendix 2: Table of excluded studies with reasons

Reference	Intervention/conditions	Reason(s) for exclusion
Reason, Population not NIU (intermediate/posterior/panuveitis)n =28		
Allegri, 2014[126]	Indomethacin in macular oedema	Includes patients with anterior and post-infective uveitis (includes other ocular disease)
Alpsoy, 2002[127]	Interferon alfa-2a in Behcet's	Not a homogenous group of patients with Behcet's uveitis
Biryukova, 2015[128]	Simvastatin	Includes patients with anterior uveitis
Blumenkranz, 2010[129]	Dexamethasone for macular oedema	Most patients did not have uveitis; no separate data
Boscia, 2005[130]	Intravitreal triamcinolone for cystoid macular oedema	Not an RCT. Not specific to uveitis
Davatchi, 2009[131]	Colchicine in Behcet's disease	Not specific to uveitis
Davatchi, 2004[132]	Cyclophosphamide in Behcet's disease	Population uveitis or retinal vasculitis, no separate data. Posterior uveitis recorded as an outcome not a population
Davatchi, 2010[133]	Rituximab in Behcet's disease	Posterior uveitis as outcome not as population
Gupta, 2013[134]	Dexamethasone in cataract	Population included patients with TB uveitis and anterior uveitis; dexa administered during cataract surgery
Kuppermann, 2007[135]	Dexamethasone in macular oedema	Patients (aged >12 years) with macular oedema; not specific to uveitis
Landewe, 2014[136]	Certolizumab pegol in axial spondyloarthritis	Only data on new cases of uveitis
Louis, 2016[137]	Adalimumab in Crohn's disease	No data for uveitis only
Perkins, 1956[138]	Pyrimethamine	Includes patients with anterior uveitis and infectious uveitis. Intervention not in scope
Roesel, 2010[139]	Triamcinolone versus prednisolone in cataract surg	Includes patients with anterior uveitis and patients undergoing cataract surgery
Roesel, 2009[140]	Triamcinolone 2 routes in cataract surgery	Includes patients with anterior uveitis and patients undergoing cataract surgery
Rosenbaum, 2004[141]	Etanercept & iritis - trials summary	Summary of iritis cases across trials of etanercept in ankylosing spondylitis
Rudwaleit, 2014[142]	Certolizumab pegol in axial spondyloarthritis	Not uveitis population. Data relates to uveitis flares - 9 cases total
Rudwaleit, 2016[143]	certolizumab pegol in axial spondyloarthritis	Not uveitis population. Data relates to uveitis flares - 7 cases total
Schlaegel, 1969[144]	Isoniazid	Mostly infectious uveitis (tuberculosis)

Reference	Intervention/conditions	Reason(s) for exclusion
Sieper, 2010[145]	Etanercept uveitis rates in trials in ankylosing spondylitis	Summary of uveitis cases across trials of etanercept in ankylosing spondylitis
Van Den Bosch, 2002[146]	Infliximab	Uveitis only reported as adverse event (in 1 patient)
Williams, 2009[147]	Dexamethasone	Patients with macular oedema due to uveitis or Irvine-Gass syndrome
Yates, 2015[148]	Etanercept in ankylosing spondylitis	Uveitis only reported as adverse event (in 3 patients)
Perkins, 1965[149]	Indomethacin	Mostly anterior, some infectious uveitis
Buggage, 2007[150]	Daclizumab in Behcet's	Uveitis or retinal vasculitis, no separate data. Daclizumab (anti-IL2) not in scope
Foster, 1996[151]	Rimexolone versus prednisolone	Anterior segment uveitis
Dada, 2007[152]	Triamcinolone post-cataract	28/40 anterior uveitis, no separate data
Parodi, 2010[153]	Bevacizumab versus photodynamic therapy	Neither in scope. For treating neovascularisation. Population multifocal choroiditis
Intervention not relevant, n=25		
Haller, 2009[154]	Dexamethasone	RCT comparing effect of insertion procedure
de Smet, 1992[155]	Cyclosporine & ketoconazole	High-dose ciclosporin versus lower dose Ciclosporin plus ketoconazole
Callanan, 2008[156]	Fluocinolone (2 doses US)	Compares to non-licensed dose
Jaffe, 2006[157]	Fluocinolone (2 doses US)	Compares to non-licensed dose
Sangwan, 2015[158]	Fluocinolone (2 doses Asian)	Compares to non-licensed dose Most data not RCT
Dick, 2013[159]	Secukinumab (3 trials versus placebo)	not in scope
Soheilian, 2013a[160]	Diclofenac versus triamcinolone in uveitic macular oedema	not in scope
Soheilian, 2010a[161]	Bevacizumab versus triamcinolone for uveitic macular oedema	not in scope
Soheilian, 2010b[162]	Bevacizumab versus triamcinolone for uveitic macular oedema	not in scope

Reference	Intervention/conditions	Reason(s) for exclusion
Rahimi, 2012[163]	Bevacizumab versus triamcinolone for uveitic macular oedema	not in scope
Farber, 1994[164]	Acetazolamide in macular oedema	not in scope
Ibrahim, 2015[165]	Sirolimus SAVE trial	not in scope
Letko, 2015[166]	Secukinumab (1 trial of 3 doses)	not in scope
Whitcup, 1996[167]	Acetazolamide in uveitic macular oedema	not in scope
Vigil, 2015[168]	Sirolimus SAVE trial	not in scope
Soheilian, 2013b[169]	Diclofenac versus triamcinolone in uveitic macular oedema	not in scope
Lashay, 2003[170]	Acetazolamide in uveitic macular oedemain Behcet's	not in scope
Van Kooij, 2006[171]	Lisinopril	not in scope
Nguyen, 2013[172]	Sirolimus SAVE trial	not in scope
Nussenblatt, 2006[173]	Vitamin E	not in scope
Nussenblatt, 1997[174]	Retinal antigens	not in scope
Neri, 2006[175]	Echinacea	not in scope
Tranos, 2006[176]	Vitrectomy	not in scope
Choi, 2005[177]	Vitrectomy versus immunomodulatory treatment	not in scope
Quinones, 2010[178]	Vitrectomy	not in scope
No relevant outcomes or data, n=15		
Bodaghi, 2001[20]	Various treatments	Retrospective analysis of causes of uveitis
Goldstein, 2007[179]	Fluocinolone	Analysis of results of 3 RCTs of Fluocinolone
Holbrook, 2016[180]	Fluocinolone (MUST trial)	Outcome, dissociation of drug pellet
Mackensen, 2008[181]	Methotrexate versus interferon in uveitic macular oedema	Secondary publication. Intermediate results only
Masuda, 1989[182]	Cyclosporin versus colchicine in Behcet's	Outcomes: “frequency of ocular attack” and “severity of ocular attack” but these are not defined
Mercante, 2007[183]	Fluocinolone (2 doses)	No comparison of data between groups
MUST, 2010[93]	Fluocinolone (MUST) study design	Secondary publication. No additional data

Reference	Intervention/conditions	Reason(s) for exclusion
Parekh, 2015[184]	Fluocinolone (intra-ocular pressure risk in 3 trials)	Analysis of results of 3 RCTs of Fluocinolone
Pavesio, 2006[185]	Fluocinolone	Secondary publication. Preliminary data. Final data in Pavesio 2010
Sheppard, 2012[186]	Fluocinolone (2 doses)	No comparison of data between groups. Secondary publication of Sangwan 2015
Waheed, 2002[187]	Etanercept (abstract)	Secondary publication of Foster 2003
Soheilian, 2007[188]	Bevacizumab versus triamcinolone for uveitic macular oedema	Secondary publication. Same study as Soheilian, 2010a+b
Muller, 2004[189]	Fluocinolone (2 doses)	In German. Duplicate publication. Same as Sangwan 2015.
Williams, 2003[190]	Dexamethasone (Posurdex)	Secondary publication of Kuppermann 2007, no results reported
Nussenblatt, 1993[191]	Cyclosporine A and G	Compares two subtypes of same drug, cannot connect to network
Not an RCT, n =33		
Abu El-Asrar, 2012[192]	Mycophenolate mofetil in VKH disease	Not an RCT
Barreiro-de-Acosta, 2012[193]		Not an RCT
Benitez-del-Castillo, 2005[194]	Infliximab	Not an RCT
Bollinger, 2009[195]	Management of intra-ocular pressure with fluocinolone implant	Review of 3 RCTs reporting adverse effects of fluocinolone acetonide
Capote, 2014[196]	Adalimumab for serpiginous choroiditis	Letter
Castellino, 1994[197]	Cyclosporine	Not an RCT
Chavis, 1992[198]	Cyclosporine	Not an RCT
Coskun, 2015[199]	Dexamethasone for Behcet uveitis	Retrospective analysis of single DEX implant (Posterior uveitis due to Behcet's Disease)
Ermertcan, 2014[200]	Adalimumab	Case report of patients with psoriatic uveitis
Giardina, 2011[201]	Infliximab in Behcet's	Not an RCT
Helveston, 1996[202]	Intravenous immunoglobulin	Case report
Jaffe, 2008[203]	Fluocinolone	Not a randomised study
Jaffe, 2000[204]	Dexamethasone	Case report

Reference	Intervention/conditions	Reason(s) for exclusion
Khalil, 2015[205]	Methotrexate in Behcet's disease	Case series
Mehryar, 2001[206]	Sulfasalazine versus cyclophosphamide in Behcet's disease	Not an RCT
MUST, 2014[207]	Fluocinolone (MUST) Cost-effectvieness	Not an RCT, Cost-effectiveness analysis
Murphy, 2007[208]	Cyclosporine versus tacrolimus	Not an RCT
Naik, 2013[209]	Dexamethasone HURON	Not an RCT. Comparison of PROMs using baseline data from HURON and national data
Ozsahin, 2012[210]	TNF inhibitor	Case report
Sen, 2016[211]	Fluocinolone (MUST)	Not an RCT. Nested cohort study of VA outcomes after cataract surgery
Sen, 2012[212]	Fluocinolone (MUST)	Not an RCT. Prevalence of hypotony at baseline in MUST
Suhler, 2013[213]	Adalimumab	Single arm study
Tay-Kearney, 2006[214]	Triamcinolone	Not an RCT. Clinical summary
Zlatanovic, 2012[215]	TNF-alpha antagonist	Not an RCT. Non-English publication (Serbian)
Frick, 2012[43]	Fluocinolone (MUST)	No RCT data, just baseline. Reports VA, and quality of life.
Sakane, 1995[216]	Tacrolimus (FK506)	Not an RCT. Also only compares doses (no placebo/other group). Same as Mochizuki 1993. Also non-English language (Japanese)
Mochizuki, 1993[217]	Tacrolimus (FK506) in Behcet's disease	Not an RCT. Also only compares doses (no placebo/other group). Same as Sakane 1995
Nguyen, 2009[218]	Fluocinolone	Not RCT. Expert perspectives
Davatchi, 2003[219]	Methotrexate in Behcet's disease	Not RCT (controlled study)
Callejas-Rubio, 2008[220]	Adalimumab	Not RCT (single arm study)
Ozyazgan, 1992[221]	Cyclosporin versus cyclophosphamide	Not RCT. Randomised but then patients could choose treatment
Hamuryudan, 1997[222]	Azathioprine in Behcet's disease	Re-analysis of patients in Yazici 1990 RCT
Denniston 2016[223]	Adalimumab	News article
Other, n = 16		
Anonymous 2012[224]	Fluocinolone (MUST)	letter to editor; erratum

Reference	Intervention/conditions	Reason(s) for exclusion
Cunningham, 2012[225]	TNF inhibitors	Editorial
Cunningham, 2010[226]	TNF inhibitors	Editorial
Farber, 1992[227]	Acetazolamide	Clinical trial record
Fraser-Bell, 2008[228]	Various	Review of treatments in patients with uveitis
Goldstein, 2009[229]	TNF inhibitors	Letter
Wirostko, 1997[230]	(Scleritis-associated uveitis)	Letter
Hall, 2015[231]	Fluocinolone	Letter to editor (difference between Retisert and Iluvien)
Zhou, 2010[232]	Traditional Chinese Medicine	Non-English language (Chinese). Intervention not in scope
Wiederholt, 1986[233]	Cyclosporin versus prednisolone	Non-English language (German). Only 8 patients and data difficult to interpret
Shimakawa, 2002[234]	Corticosteroids (oral versus topical)	Non-English language (Chinese). Likely non-RCT
Puchalska-Niedbal, 1989[235]	FIBS preparation	Non-English language (Polish). Some patients with infectious uveitis, unlikely to be relevant intervention
Masuda, 1986[236]	Cyclosporin	Non-English language (Chinese). Other report of this study (Masuda 1989) was excluded as outcomes not sufficiently robust
Rho, 1996[237]	Acetazolamide	Letter
Gonzalez 2005[238]	Fluocinolone	Editorial
Lai, 2005[239]	Periocular corticosteroids	Letter

Appendix 3: Data extraction form

Reviewer:			
Study Reference	Study Name	Author year	Setting(s)
STUDY POPULATION			
Inclusion and Exclusion criteria:			
Age:		Percentage, males:	
Sample size *(number of patients randomised)*		Sample size *(number of eyes randomised)*	
Type of uveitis: *(intermediate uveitis, posterior uveitis, panuveitis/ active, non-active/ bilateral or unilateral)*			
Cause of uveitis: *('known systemic condition'; 'no known systemic condition', 'not reported', 'unclear')*			
State known systemic condition (s):			
Prior treatment received (including treatment for any associated systemic condition): yes/no			
List prior treatment(s):			
Concomitant treatment(s): *('ALL' if treatment was received by all patients or 'PRN' if treatment was given as needed)*			
List concomitant treatment(s):			
Baseline best corrected visual acuity:		Baseline intraocular pressure:	
Baseline VH grade:		Baseline central macular thickness:	
OUTCOMES			
Outcomes reported in the study		Follow-up schedule for assessments	
TREATMENT ARM AND COMPARATOR ARM			
Allocated treatment *(dosing routine and duration of treatment)*:			
Number randomised *(patients/eyes)*:			
Number analysed *(patients/eyes)*:			
Details of any excluded/lost/withdrew post randomisation and reasons:			
*Vision or visual acuity outcomes reported :			
*Outcomes of intraocular inflammation activity (e.g. VH grade or AC cell grade) reported:			
*Reported outcomes of uveitis-related tissue damage or complication (e.g. cataract, macular oedema):			
*Other outcomes reported (e.g. composite outcomes):			
*Patient-reported outcomes reported:			
*Ocular and systemic adverse effects reported:			
RELEVANCE FOR NETWORK META-ANALYSIS			
Clinically relevant? yes/no			
Connects relevant treatments via network: yes/ no			

PRN, *pro re nata*
*Comparisons between study arms were abstracted or calculated.

Appendix 4: Criteria for assessment of methodological quality of included studies

Quality item	Reviewer's judgement	Details
1: Were participants assigned to study groups using an acceptable random method?	Yes	Use of centrally-generated random numbers; random number tables; throwing dice
	No	Use of case record numbers, date of birth or alternation or rotation
	Unclear	Insufficient details to assess quality item
2: Was allocation concealment adequately conducted?	Yes	Allocation to study arms achieved by using interactive or we-based system; sequentially numbered opaque envelopes
	No	Allocation to study arms achieved without appropriate measures e.g. unsealed, transparent envelopes, date of birth, alternation or rotation or other unconcealed methods
	Unclear	Insufficient details to assess quality item
3: Were eligibility criteria specified for selecting participants?	Yes	Eligibility criteria of study participants specified at study entry
	No	Eligibility criteria of study participants, not specified at study entry
	Unclear	Insufficient details to assess quality item
4: Was the study adequately powered?	Yes	Sample size considered to be adequate (i.e. at least 80% or more) based on a priori sample size calculation and significance level to detect a minimally clinical significant difference in primary outcome of interest
	No	Sample size considered to be inadequate (i.e. less than 80%) based on a priori sample size calculation and significance level to detect a minimally clinical significant difference in primary outcome of interest
	Unclear	Insufficient details to assess quality item
5: Were study groups comparable for most prognostic indicators at baseline?	Yes	Key prognostic variables (e.g. age, visual acuity, intraocular pressure) were reported to be similar in relevant treatment groups at baseline.
	No	Key prognostic variables (e.g. age, visual acuity, intraocular pressure) were reported to be different between relevant treatment groups at baseline.
	Unclear	Insufficient details to assess quality item
6: Were patients and investigators/outcome assessors blinded to treatment allocation?	Yes	Patients, investigators and/or outcome assessors could not identify administered study treatments.
	No	Patients, investigators and/or outcome assessors may possibly identify administered study treatments.
	Unclear	Insufficient details to assess quality item
7: Was follow-up adequate (≥70% randomised patients analysed)?	Yes	At least 70% of randomised patients (or eyes) were included in the analysis.
	No	Less than 70% of randomised patients (or eyes) were included in the analysis.
	Unclear	Insufficient details to assess quality item

8: Were reasons for attrition /exclusions stated?	Yes	Number of patients lost to follow-up (including withdrawals and those excluded from analysis) were reported to ensure completeness of data
	No	Incomplete data reporting noted because number of patients lost to follow-up (including withdrawals and those excluded from analysis) were not reported.
	Unclear	Insufficient details to assess quality item
9: Was an intention-to-treat analysis included?	Yes	Outcome data for all patients initially randomised to a specific study arm were included in the analysis of the specified outcome.
	No	Outcome data for selected patients initially randomised to a specific study arm were included in the analysis of the specified outcome.
	Unclear	Insufficient details to assess quality item

Appendix 5: Effectiveness data from non-randomised studies of dexamethasone implant

Ref Design	N, FU Implants	BCVA	Vitreous haze (VH)	Central retinal thickness (CRT)	Repeat implantations	Other
Tomkins-Netzer et al., 2014[22] Retrospective review of treatment and re-treatment with DEX 700 for non-infectious uveitis, 2 centres, UK	27 pts 38 eyes 24 mo 1: 14 eyes 2: 14 eyes 3: 7 eyes 4: 2 eyes 6: 1 eye	Mean BCVA improved significantly after first implantation, from baseline of 0.47 (SEM 0.05) logMAR (Snellen 20/60) to 0.27 (0.07) logMAR (20/37) at 2 months (P < 0.001); deteriorated to 0.43 (0.12) logMAR (20/54) by 6 months	Significant improvement in % eyes with VH=0 after first implantation, from 58% at baseline to 83% at 1 month (P = 0.03); remained until month 6 (85%, P = 0.02) but decreased by 12 months (53%)	Mean (SEM) CRT decreased significantly from 453 (SEM 34) µm at baseline to 263 (44) µm at 1 month after first implantation (P = 0.003). Macular oedema persisted in 50% of eyes, but remaining eyes had decrease in CRT of 127 (52) µm at 6 months (P = 0.01); improvement maintained to 12 months	BCVA: 2nd implant: improved from 0.55 (0.1) logMAR (20/70) to 0.22 (0.07) logMAR (20/33) at 1 month (P = 0.004), decreased after 1 month. 3rd implant: similar trend, not significant. 4th implant: BCVA improved from 0.83 (0.17) logMAR (20/135) at baseline to 0.32 (0.09) logMAR (20/42) at 1 month. One eye had 6 implants: improved BCVA within 1 mo. CRT: After 2nd implant, decreased by 187 (52.9) µm at 2 months (P = 0.043). 3rd implant: CRT improved but not sig. 4th implant: decrease of 225.67 [109.85] µm at 1 month. VH: Improvement in % with VH=0 after 2nd implant not significant (72.7% at baseline, 91.7% at 1 mo); similar trend after 3rd implant	Median time to relapse: 6 mo (range 2–42 mo) after 1st implant; relapse in 69% eyes. After 2nd implant: 6 mo (1–12 mo); relapse in 48% eyes. Reducing other treatment: After 1st implant: systemic or local treatment reduced or stopped in 33 eyes of 21 (78%) patients. Implants in both eyes: 11 pts had implants in both eyes; 2nd implant administered 113 ± 32 days after first. 3 of 11 patients had a response in the second eye (reduced CRT; improved BCVA.
Zarranz-Ventura et al., 2014[48] Retrospective review of DEX 700 for non-infectious uveitis, multicentre, UK & Spain	63 pts 82 eyes Mean 15.4 mo 1: 43 eyes 2: 24 eyes ≥3: 15 eyes	Mean VA was 0.68 (SD 0.4) logMAR (Snellen 20/90) at baseline, improving to 0.59 (0.4) logMAR (20/78) after 2 weeks, 0.49 (0.4) logMAR (20/62) at 1 month, 0.49 (0.5) logMAR (20/62) at 3 months, 0.60 (0.5) logMAR (20/80) at 6 months, and 0.52 (0.5) logMAR (20/66) at 12 months (all P < 0.01)	VH only analysed in 39 eyes with vitritis at baseline (VH ≥ +0.5). Probability of VH improvement (2-step or change +0.5 to 0) was 41% at 2 weeks, 63% at 1 month, 73% at 3 months, 79% at 6 months and 88% at 12 months. The median time to improvement in VH was 1 month (95% CI 0.6–1.3).	CRT only analysed in 59 eyes with CMO. Mean CRT 469 (SD 193) µm at baseline, improving to 326 (81) µm at 2 weeks, 267 (74) µm at 1 month, 318 (149) µm at 3 months, 366 (140) µm at 6 months, and 355 (160) µm at 12 months (all P < 0.01).	Median time to second implant: 10 months (95% CI 6.3–13.6).	Concomitant systemic immunosuppressants or corticosteroids: Probability of dose reduction (≥5 mg steroids or any reduction in immunosuppressants) was 36% at 1 month, 42% at 3 months, 46% at 6 months, and 62% at 12 months. Probability of steroid discontinuation: 8% at 1 and 3 months, 11% at 6 months, and 36% at 12 months.

Ref Design	N, FU Implants	BCVA	Vitreous haze (VH)	Central retinal thickness (CRT)	Repeat implantations	Other
Miserocchi et al., 2012[63] Retrospective study of DEX 700 for posterior uveitis, single centre, Italy	12 pts 14 eyes 11 mo 15 implants in 14 eyes	Mean BCVA was 20/80 (0.6 logMAR) before implant and 20/40 (0.3 logMAR) at end of follow-up (6–11 months). Mean improvement in BCVA of 3.3 lines at end of follow-up (range 0–6 lines)	NR	CRT was 496 (123) µm at baseline and improved to 226 (66) µm by end of follow-up.	NR	Concomitant systemic immunosuppressants or corticosteroids: All patients on systemic immunosuppressants or corticosteroids. 3/12 patients reduced corticosteroid dose after receiving DEX 700.
Palla et al., 2015[64] Retrospective review of DEX 700 for non-infectious uveitis, single centre, India	15 pts 20 eyes 12 mo NR	Mean BCVA improved from 0.666 logMAR (Snellen 20/93) at baseline to 0.479 logMAR (20/60) at 6 weeks (stated as statistically significant)	Proportion achieving VH=0 was 60%, 45%, and 30% at 6 weeks, 6 months, and the last visit, respectively.	Mean CRT improved from 563.1 µm at baseline to 361.4 µm at 6 weeks. Trend continued at each follow-up. Two eyes with epiretinal membrane at baseline had minimal CRT improvement	NR	NR
Lam et al., 2015[65] Retrospective review of DEX 700 for macular oedema, multicentre, Canada	20 pts 23 eyes 1-6 mo Mean implants: 1.7 ± 0.2	After 1st implant, 17/21 eyes (81%) gained ≥ 1 line of vision, 13 (62%) gained ≥ 2 lines, and 12 (57%) gained ≥ 3 lines.	NR	17/ 23 eyes had improvement in CRT, mean peak improvement of 255.6 (SE 43.6) µm. Eyes without prior PPV showed greater mean peak improvement than eyes that had (295.1 ± 54.0 µm versus 161.0 ± 20.4 µm).	Mean (± SE) number of implants was 1.7 ± 0.2. Mean time from 1st to 2nd implant was 4.7 ± 0.3 months, and mean time from 2nd to 3rd implant was 3.4 ± 0.4 months. BCVA: After 2nd implant, 9 (90%), 7 (70%), and 5 of 10 eyes (50%) gained ≥ 1, 2, or 3 lines of vision, respectively. After 3rd implant, 4/5 eyes (50%) gained ≥ 3 lines of vision	NR

Ref Design	N, FU Implants	BCVA	Vitreous haze (VH)	Central retinal thickness (CRT)	Repeat implantations	Other
Pleyer et al., 2014[66] Prospective case series, single DEX 700 implant intermediate or posterior uveitis, 2 centres, Germany	84 pts 84 eyes 6 mo NR	Mean BCVA 0.68 ± 0.47 logMAR (Snellen 20/100) at baseline; improved to 0.53 ± 0.54 logMAR (20/63) by 4 weeks (P = 0.001) and to 0.51 ± 0.49 logMAR (20/63) by 12 weeks (P < 0.001). BCVA improvement lost by week 24 (P = 0.999)	% with VH=0 increased from baseline at 4 weeks (61% versus 19%; P < 0.001); remained significantly above baseline throughout follow-up. Mean VH remained below baseline (P < 0.001 at weeks 4, 12 and 24)	Mean CRT improved from 463 ± 165 µm at baseline to 300 ± 110 µm by week 4 (P < 0.001). Improvement remained significant throughout the follow-up period (P < 0.001 at 12 and 24 weeks).		Concomitant systemic immunosuppressants or corticosteroids: 32 patients (38%) on systemic immunosuppressants (+/- corticosteroids) at baseline. Systemic corticosteroids discontinued in 8 (25%) and reduced (to < 10 mg) in a further six (19%)
Nobre-Cardoso et al., 2016[67] Retrospective review of DEX 700 for non-infectious uveitic macular oedema, single centre, France	31 pts 41 eyes 12 mo 1: 18 2: 10 3: 2 4: 1	Significant improvement in mean BCVA at 1 month after first implant, from 0.84 ± 0.81 logMAR (Snellen 20/140) at baseline to 0.74 ± 0.84 logMAR (20/110) (P < 0.01). Mean BCVA remained improved from baseline at 12 mo	% with VH=0 increased from 51.2% at baseline to 71.1% at month 1 (P < 0.001), and 75.6% at month 3 (P < 0.01). % with VH=0 at month 12 was higher than at baseline (64.7%).	After 1st implant, sig improvement in mean CRT: 461 ± 158 µm at baseline to 308 ± 93 µm at 1 mo (P < 0.001). At 3 mo, mean CRT 340 ± 110 µm (P < 0.001). At 6 mo, 442 (± 172 µm). After one implant, six eyes free of relapse in MO at 12 mo	In 13 eyes with relapse after a positive response to first implant, mean time to second implant was 7.1 ± 2.9 months after first. Repeat implantations improved BCVA (+ 0.08 logMAR) and CRT (304 µm decrease) at 1 month post-implant. After repeat implant, mean time to relapse 5.0 ± 1.6 months, similar to first (P = 0.689).	Mean time to relapse: after first implant (increase ≥ 50 µm in CRT from month 1) was 6.7 ± 3.7 months. At 12 months, the overall relapse rate was 83.3%.
Tsang et al., 2016[68] Retrospective review of DEX 700 for uveitic macular oedema in Canada	15 pts 25 eyes 12 mo Single: 18 eyes Repeat: 7 eyes	BCVA improved in 20/25 eyes (80%). Significant improvement in mean BCVA at 3 months, from 0.614 ± 0.089 logMAR (Snellen 20/82) at baseline to 0.35 ± 0.10 logMAR (20/45) at month 3. Five of 25 eyes (20%) had worsening of VA during follow-up.	NR	CRT improved in 32/35 eyes (91.4%), from 590 ± 28 µm at baseline to 380 ± 28 µm at 1 month and 370 ± 3 µm at 3 months (P < 0.001); maintained throughout follow-up	For 7 eyes with repeat implant: BCVA improvement at 1 month after 1st implant 0.069 ± 0.179 logMAR; after 2nd implant 0.184 ± 0.171 logMAR (diff not significant). CRT reduced by 268 ± 76 µm at 1 mo after 1st implant; 291 ± 74 µm at 1 mo after repeat implant (diff not significant) Median time to treatment failure (increase in CRT > 10% and ≥ 50 µm, or need for repeat implant) was 6 mo	NR

Ref Design	N, FU Implants	BCVA	Vitreous haze (VH)	Central retinal thickness (CRT)	Repeat implantations	Other
Adan et al., 2013[69] Retrospective study of DEX 700 after vitrectomy for uveitic macular oedema, Spain	13 pts 17 eyes 12 mo Single: 9 eyes Repeat: 8 eyes	Median improvement in BCVA at 1 month was 1 line (range 0–3; n = 15 eyes; P < 0.01), increasing to 2 lines by 3 months; 52.9% of eyes improved by ≥ 2 lines (P < 0.01). Improvement was maintained in 5 eyes (29.4%) at 6 months. No eyes lost > 1 line of BCVA from baseline (P = 0.003)	NR	Mean CRT at baseline 461.6 (SD 121.7) µm; decreased to 277.2 (66.5) µm at 1 month (P < 0.01); at 3 months (349.9 [143.2] µm, P = 0.01) at 6 months 394.1 [138.4] µm (P = 0.14). Reduction in CRT > 100 µm in 10 eyes (62%) at 1 mo, eight eyes (47.1%) at 3 mo, and five eyes (29.4%) at 6 mo	NR	Duration of response: Over follow-up (mean 9.6 mo; range 6–17), relapse of CMO (CRT increase > 150 µm from lowest post-implant) in 8 of 17 eyes (47.1%) after mean of 6.5 months (3–11 mo). These eyes had repeat implant
Pelegrin et al., 2015[49] Retrospective review of DEX 700 for macular oedema secondary to non-infectious uveitis, single centre, Spain	32 pts 42 eyes 24 mo 1: 23 eyes 2: 12 eyes 3: 5 eyes 4: 2 eyes	BCVA improved in vitrectomised and non-vitrectomised eyes. Max improvement at month 3 in both groups, maintained throughout follow-up. Difference between vitrectomised and non-vitrectomised statistically significant only at 24 months (favoured non-vitrectomised, P = 0.04).	VH at baseline +0.5 to +3.0 in 21 eyes (50%). Two-step improvement or change from +0.5 to 0 in 66.7% at 1 month, 62% at 3 months, 76.2% at 6 months and 80.1% at 12 months. Changes in max VH score similar in non-vitrectomised and vitrectomised eyes in all follow-up (P = 0.706)	Max decrease in CRT at month 1 in non-vitrectomised and vitrectomised eyes (251.2 and 229.9 µm). Maintained through follow-up: at 24 months mean CRT improved by 189.1 and 273.8 µm in non-vitrectomised and vitrectomised eyes (diff significant only at 24 months, P = 0.02)	Repeat implants required in 19 eyes (45.2%). No difference in frequency of repeat implants between non-vitrectomised and vitrectomised eyes. Median time to repeat implantation was 5 months (IQR 5–6 months). Twelve eyes (28.6%) required two implants, five (11.9%) required three implants, and two(4.8%) had four implants.	Concomitant systemic corticosteroid treatment: At baseline, 40.3% receiving systemic prednisone and 53.1% second-line agents. Prednisone reduced to < 10 mg/day in all patients at 1 month; dose reduction maintained in 78% at 12 months. Discontinuation of prednisone in 31.8% at 12 mo

Ref Design	N, FU Implants	BCVA	Vitreous haze (VH)	Central retinal thickness (CRT)	Repeat implantations	Other
Khurana and Porco 2015[70] Retrospective review of DEX 700 for cystoid macular oedema secondary to non-infectious uveitis, single centre, US	13 pts 18 eyes 3 mo 1: 8 eyes 2-4: 10 eyes	Mean BCVA at baseline 0.449 logMAR (Snellen 20/60); improved to 0.238 logMAR (20/30) by 1 mo. Sig. improvement at 1 mo (2.0 lines; P = 0.0016), 3 months (2.1 lines; P = 0.0051), 6 months (2.1 lines; P = 0.014) and 12 months (1.4 lines; P = 0.11). Improvement ≥ 2 lines in 47% of eyes at 1 mo and 50% at 3 mo	Baseline VH was grade 1 in 33% of eyes and grade 2 in 11%. VH was grade 0 at 1, 3, 6, and 12 months of follow-up.	After 1st implant, complete resolution of CMO in 89% eyes at 1 mo; 72% at 3 mo. In eyes without epiretinal membrane, CRT decreases at 1 mo (190 µm;P = 0.00048) and 3 mo (228 µm; P = 0.0039). In eyes with epiretinal membrane, mean change not significant at 1 mo (100 µm; P = 0.063) or 3 mo (33 µm; P = 0.50). In all patients, median time to CMO recurrence 201 ± 62 (SE) days)	Repeat implantation in patients with recurrence of CMO and decrease in VA from previous visit. Number of implants per patient during follow-up ranged from 1 to 4; 56% (10 of 18 eyes) needed two or more implants. Among those with second implant, median time to re-treatment was 300 ± 71 days.	
BCVA, best-corrected visual acuity; CMO, cystoid macular oedema; CRT, central retinal thickness; FU, follow-up; logMAR, logarithm of the Minimum Angle of Resolution; N, number of patients; pts, patients; SE, standard error; VH, vitreous haze						

Appendix 6: Safety data from non-randomised studies of dexamethasone implant

Ref	Design	N	Follow-up	N implants	Increased IOP	Cataracts	Other adverse events
Tomkins-Netzer et al., 2014[22]	Retrospective review of treatment and re-treatment with DEX 700 for non-infectious uveitis, 2 centres, UK	27 pts 38 eyes	24 mo	1: 14 eyes 2: 14 eyes 3: 7 eyes 4: 2 eyes 6: 1 eye	- First implant: 3 eyes had IOP >21 mmHg within 2 months - Second implant: 4 eyes had IOP > 25 mmHg within 2 months - Third implant: no increased IOP - Frequency of increased IOP: 0.13 per eye-year	- First implant: cataract in 1/21 phakic eyes - Second implant: no new cataracts - Third implant: 1 further cataract	Implant migration in 1 eye that had undergone cataract extraction
Zarranz-Ventura et al., 2014[48]	Retrospective review of DEX 700 for non-infectious uveitis, multicentre, UK & Spain	63 pts 82 eyes	12 mo	1: 43 eyes 2: 24 eyes ≥3: 15 eyes	- IOP ≥21 mmHg in 33/82 eyes (40.2%) - IOP ≥35 mmHg: 7% at months 1&3 - IOP-lowering medication required in 32 (39%)	- Cataract surgery in 4/40 (10%) phakic eyes during follow-up	- Implant migration to AC: 2/142 (1.4%), one aphakic eye, one pseudophakic eye - Vitreous haemorrhage: 3 (2.1%) - Hypotony: 3 (2.1%) - Endophthalmitis: 1 (0.7%)
Miserocchi et al., 2012[63]	Retrospective study of DEX 700 for chronic posterior non-infectious uveitis, single centre, Italy	12 pts 14 eyes	11 mo	15 implants in 14 eyes	- Raised IOP in 3/14 eyes (21%) within 2 weeks, all transient, all controlled with topical IOP-lowering medication	- No cataracts or cataract surgery reported	- Subconjunctival haemorrhage: 1 case - Vitreous haemorrhage: 1 case in patient on anticoagulants
Palla et al., 2015[64]	Retrospective review of DEX 700 for non-infectious uveitis, single centre, India	15 pts 20 eyes	12 mo	NR	- IOP > 21 mmHg in 3 (15%) and IOP ≥ 25 mmHg in 2 (10%) by week 6 - All manageable with medication	- Cataract surgery: 2 (10%) within 6 months; 5 (25%) within 1 year	- Pars planitis: 1 (5%)
Lam et al., 2015[65]	Retrospective chart review of DEX 700 for macular oedema, multicentre, Canada	101 pts 120 eyes	1-6 mo	Mean implants: 1.7	- Raised IOP in 2/20 (10%) - Of eyes with a history of steroid response, 37.5% had IOP ≥25 mmHg and 12.5% had IOP ≥35 mmHg - Topical IOP-lowering medications required for 62.5% of eyes with a history of steroid response	- Cataract: 1/11 (9%) phakic eyes - Cataract surgery: 5/11 (46%) phakic eyes	- Retinal detachment: 1/20 (5%) - Serious uveitis flare: 1/20 (5%)

Ref	Design	N	Follow-up	N implants	Increased IOP	Cataracts	Other adverse events
Nobre-Cardoso et al., 2016[67]	Retrospective review of DEX 700 for non-infectious uveitic macular oedema, single centre, France	31 pts 41 eyes	12 mo	1: 18 2: 10 3: 2 4: 1	- IOP > 21 mmHg in 36% - IOP > 25 mmHg in 31% - IOP >30 mmHg in 6.9% - All cases responded to topical IOP-lowering medication - Ocular hypertension: 15 eyes, 10 had history of steroid response	- Cataract surgery: 3 eyes (all with repeat implants)	- Vitreous haemorrhage: 1 case, patient on antiplatelet medication
Pleyer et al., 2014[66]	Prospective case series of single DEX 700 implant for non-infectious intermediate or posterior uveitis, 2 centres, Germany	84 pts 84 eyes	6 mo	NR	- IOP ≥25 mmHg: 13 (16%) - IOP ≥35 mmHg: 3 (4%) - IOP-lowering medication: 21% at baseline, 42% at 12 wk, 28% at 24 wk - Stronger IOP increase in intermediate over posterior uveitis (p=0.003)	- Cataract: 7 phakic eyes - Pre-existing cataracts progressed in 2/3 - No surgery required	- Conjunctival haemorrhage in "few patients (n NR), cleared rapidly - No cases endophthalmitis or uveitis flare-up
Tsang et al., 2016[68]	Retrospective review of DEX 700 for uveitic macular oedema in Canada	15 pts 25 eyes	12 mo	Single: 18 eyes Repeat: 7 eyes	- No patients had IOP >21 mmHg or increase of >10 mmHg (patients with IOP >21 mmHg were excluded)	- No new cataracts - Pre-existing cataracts progressed in 2/15	- Implant injected into lens in 1 eye - Macular hole: 1 - Epiretinal membrane: 3 - No cases of endophthalmitis or retinal detachment
Adan et al., 2013[69]	Retrospective study of DEX 700 after vitrectomy for uveitic macular oedema, Spain	13 pts 17 eyes	12 mo	Single: 9 eyes Repeat: 8 eyes	- IOP 22-30 mmHg: 41% - IOP 30-40 mmHg: 1 (6%) - IOP >40 mmHg: 0 - All treated with topical medication and normalised within 8 wk - Surgery for IOP: 1 patient	- Cataract surgery for pre-existing cataract: 1 (6%)	- Hypotony (transient, resolved without treatment): 2 (12%) - Retinal detachment: 1 (6%), 5 months post-implant - No cases of endophthalmitis or vitreous haemorrhage
Pelegrin et al., 2015[49]	Retrospective review of DEX 700 for macular oedema secondary to non-infectious uveitis, single centre, Spain	32 pts 42 eyes	NR	1: 23 eyes 2: 12 eyes 3: 5 eyes 4: 2 eyes	- IOP >21 mmHg: 20 (48%) – 8 non-vitrectomised eyes (36.4%) and 12 vitrectomised eyes (60%) - New hypotensive treatment required in 9 eyes	- Pre-existing cataracts progressed in 4/4; 3 required surgery	- Implant migration to AC: 2 eyes (4.7%; one aphakic, one with iris-claw intraocular lens) - Hypotony (transient, resolved without treatment): 3 (7.1%) - Vitreous haemorrhage: 3 (7.1%)

Ref	Design	N	Follow-up	N implants	Increased IOP	Cataracts	Other adverse events
Khurana and Porco 2015[70]	Retrospective review of DEX 700 for cystoid macular oedema secondary to non-infectious uveitis, single centre, US	13 pts 18 eyes	3 mo	1: 8 eyes 2-4: 10 eyes	- IOP ≥25 mmHg: 2 (11%) over 3 mo - IOP ≥35 mmHg: 0 - All managed with topical medications - None required surgery	- Progression of pe-existing cataract: 1/10 phakic eyes	- No cases of retinal detachment, hypotony, or migration of implant to AC - No serious AEs

AE, adverse effect; IOP, intra-ocular pressure; N, number

Appendix 7: Characteristics of studies included in the cost-effectiveness review

Author	Padula *et al.* [94]	Sugar *et al.* [95]
Country & year of publication	USA, 2011	USA, 2014
Type of economic analysis	CUA	CUA
Health economic perspective	Societal	Payer's perspective for costs and the patient's perspective for outcomes.
Health economic comparisons (listed interventions)	Infliximab Systemic steroids Methotrexate	Fluocinolone acetonide intraocular implant Oral corticosteroid with immunosuppressive agents as needed
Population characteristics	Patients with sarcoid posterior uveitis.	Patients aged 13 years or older with non-infectious intermediate, posterior, or panuveitis in one or both eyes (active within <= 60 days) for which systemic corticosteroids were indicated (excluding those requiring systemic therapy for non-ocular indications)
Time horizon	Lifetime	3 years
Health economic outcomes	Cost per QALY gained	Cost per QALY gained
Modelling approach	Extrapolation of trial data	Semi-Markov model

Appendix 8: Breakdown of the cost-effectiveness analysis results for the base case

Table 66: Breakdown of the results of the base case analysis for dexamethasone versus limited clinical practice (deterministic)

	Sham	Dexamethasone	Incremental
LYs			
On treatment	18.708	18.745	0.036
Blind	2.025	1.989	-0.036
Total	20.734	20.734	0.000
QALYs			
On treatment	13.932	13.976	0.044
Blind	0.774	0.760	-0.014
Total	14.706	14.736	0.030
Costs			
Drug costs	£2,454.77	£3,329.51	£874.74
Admin. and monitoring	£17,489.34	£17,636.71	£147.37
AEs	£5,197.31	£5,266.64	£69.33
Rescue therapy	£285.86	£35.33	-£250.53
Blindness	£15,542.23	£15,264.87	-£277.36
Total	£40,969.50	£41,533.06	£563.57
ICER (£/QALY)			**£18,877.62**

Table 67: Breakdown of the results of the base case analysis for adalimumab versus limited clinical practice in patients with active uveitis (deterministic)

	Placebo	Adalimumab	Incremental
LYs			
On treatment	0.620	2.085	1.464
Failed treatment	18.103	16.824	-1.278
Remission	0.000	0.000	0.000
Blind	2.011	1.825	-0.186
Total	20.734	20.734	0.000
QALYs			
On treatment	0.525	1.803	1.278
Failed treatment	14.007	12.972	-1.036
Remission	0.000	0.000	0.000
Blind	0.680	0.616	-0.065
Total	15.212	15.390	0.178
Costs			
Drug costs	£2,896.74	£22,078.30	£19,181.56
Admin. & monitoring	£18,897.02	£19,324.76	£427.74
AEs	£8,274.71	£8,562.39	£287.68
Blindness	£15,430.02	£13,984.93	-£1,445.09
Total	£45,498.50	£63,950.39	£18,451.89
ICER (£/QALY)			**£ 103,837.28**

Table 68: Breakdown of the results of the base case analysis for adalimumab versus limited clinical practice in patients with inactive uveitis (deterministic)

	Placebo	Adalimumab	Incremental
LYs			
On treatment	2.946	4.236	1.290
Failed treatment	15.777	14.693	-1.084
Remission	0.000	0.000	0.000
Blind	2.011	1.805	-0.206
Total	20.734	20.734	0.000
QALYs			
On treatment	2.466	3.531	1.064
Failed treatment	12.447	11.551	-0.896
Remission	0.000	0.000	0.000
Blind	0.680	0.609	-0.072
Total	15.594	15.690	0.096
Costs			
Drug costs	£5,169.97	£44,146.02	£38,976.05
Admin & monitoring	£20,66[illegible]	£21,378.[illegible]	£71[illegible].84
AEs	£4,501.[illegible]2	£4,146.2[illegible]	-£3[illegible]4.86
Blindness	£15,424.83	£13,844.55	-£1,580.28
Total	£45,759.68	£83,515.43	£37,755.75
ICER (£/QALY)			**£392,599.51**

National Institute for Health and Care Excellence

Multiple Technology Appraisal

Adalimumab and dexamethasone for treating non-infectious uveitis [ID763]

AbbVie's Response to the Assessment Group's Report

Adalimumab and dexamethasone for treating non-infectious uveitis [ID763]08 February 2017

Dear Meindert,

AbbVie welcome the opportunity to comment on the report produced by the Assessment Group for the ongoing Multiple Technology Appraisal of adalimumab and dexamethasone for treating non-infectious uveitis [ID763].

Please find our comments summarised below.

With kind regards,

Antonia Morga

Senior HTA Manager, AbbVie UK Ltd.

Issue 1. Vision loss rates may not be accurate

Description of the issue: In the model the rate of vision loss is assumed to be 6.6% per decade throughout the model time-horizon.

AbbVie believe that the rate of blindness in uveitis patients could be higher than the one reported by Dick et al[1] and hence not appropriate to be used as a starting point to assess the rate in the UK. The Dick et al[1] analysis was conducted among non-elderly US patients with commercial insurance (i.e. well covered under US health plans) who were receiving anti-TNF with or without immunotherapy ([redacted] of all patients), immunotherapy without biologics ([redacted]) or steroids alone ([redacted] [i])[2]. The high rate of biologic use in the Dick et al patient population does not reflect treatment practice in the UK. Therefore, the rate of blindness in this population is likely to be lower than that in the UK, due to the higher rate of aggressive therapy and younger patient age[ii].

AbbVie believe that the rate of blindness noted in the Durrani study[3] may be more realistic given the types of uveitis in the VISUAL I and II trials. Most patients in the VISUAL studies had pan-uveitis or posterior uveitis which are associated with poor outcomes. It should also be noted that Durrani is a UK study (retrospective review of medical records of 315 consecutive patients attending a tertiary referral uveitis service at the Birmingham and Midland Eye Centre over a 2 year period, January 1998 to December 2000) reflecting UK practice.

Table 1 below illustrates the distribution of patient types at baseline in the references mentioned by the Assessment Group. Patients from Durrani et al more closely resemble the patients included in VISUAL I and II trials. In particular, the proportion of patients with pan-uveitis is very similar in Durrani et al and the VISUAL I and II trials. However, no information is provided for the distribution of patient type in the Dick et al population from the US.

Table 1: Distribution of patient type by study

	Durrani et al (2004)[3]	Tomkins-Netzer et al (2014)[4]	VISUAL I[5]	VISUAL II[6]
Anterior	26%	30%	0%	0%
Intermediate	10%	33%	22%	21%
Posterior	3%	0%	34%	32%
Pan-uveitis	47%	0%	45%	46%
Posterior/pan	50%	37%	79%	78%
Other	13%	0%	0%	0%
Age	7-86		18-81	

AbbVie believe that the patients in Durrani et al[3] are the closest match to the patients from VISUAL I and II. In fact, patients in the VISUAL I and II are likely to demonstrate more

[i] Medication use was classified into mutually exclusive categories based on the following hierarchy: 1) patients were treated with biologic; 2) patients were treated with immunosuppressant therapies but not a biologic; 3) patients were treated with corticosteroids but not biologic or immunosuppressant therapy.

[ii] Patients older than 64 were not part of the analysis or followed up as those patients would be covered by the Medicare program (outside of the dataset used in the Dick et al analysis).

severe uveitis characteristics than patients in the Durrani et al[3] paper and perhaps even much more severe than those seen in the Tomkins-Netzer et al[4] study.

Proposed amendment: The rate of vision loss from the Durrani et al paper[3] should be used as the base case in the analysis. This study shows that the rate of WHO-defined blindness is 36/315 patients over 3.06 years. However, this rate only considers the rate of legal blindness. In order to reflect the disease course, the rate of bilateral permanent moderate and/or severe vision loss should be used: 46/315 patients over 3.06 years. Presumably, 10 of these 46 patients experience a moderate vision loss, while 36 experience a severe vision loss.

Alternatively, the article by Tomkins-Netzer et al (2004)[4] showed that the risk of vision loss was significantly higher in patients with non-anterior uveitis than those with anterior uveitis: adjusted relative risk (95% CI) for severe vision loss = 1.62 (1.03-2.54, p=0.04) and for moderate vision loss = 1.5 (1.11-2.02, p=0.008). If the risk of 1.62 is applied to the Durrani et al[3] paper, knowing the number of patients with WHO-level blindness and the number of patients in the two categories (anterior, n=81; non-anterior n=234), then we can derive the rate of blindness in both groups as follows:

Table 2: Calculated rate of blindness for both anterior and non-anterior uveitis

	Cases	N	% blind
Anterior	6.34	81	7.82%*
Non-anterior	29.66	234	12.68%*
All	36	315	11.43%

*The ratio of 12.68 over 7.82 is equal to 1.62

Thus, AbbVie believe that the rate of blindness should be higher than the rate of vision loss assumed in the model (6.6% per decade). AbbVie suggest that the rate of blindness should be closer to 12.7% and no less than 11.4% over 3.06 years.

Possible likely impact on ICER: Using the rate of blindness (36/315 over 3.06 years) from the Durrani paper, the ICER for active uveitis decreases to £33,003 while the ICER for inactive uveitis decreases to £85,544.

Alternatively, if it is further assumed that the rate of vision loss for those with non-anterior uveitis is actually faster than those with anterior, as reported in Tomkins-Netzer[4] (adjusted relative risk 1.62), then the rate of blindness in the Durrani et al[3] paper for the non-anterior uveitis patients would be 12.68% (please refer to calculations above). Using the latter, the ICER for active uveitis decreases to £30,852 while the ICER for inactive uveitis decreases to £80,843.

Issue 2. Discontinue treatment with adalimumab in patients in quiescence (drug induced disease remission) is not included in the base case model

Description of the issue: Currently, the model's base case analysis treats patients with adalimumab until they fail on treatment. It should be noted that in clinical practice ocular status is regularly assessed to decide whether or not ongoing medication is needed.

The Assessment Group carried out an explanatory analysis assuming that all patients discontinue adalimumab after 2 years of quiescence. This explanatory analysis is also broadly in line with the current labelling for adalimumab in uveitis which recommends that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis (see section 5.1 of SmPC for adalimumab[7]).

Indeed, the interim guidance issued by the All Wales Therapeutics and Toxicology Centre (AWTTC) for the treatment of adult patients with severe refractory non-infectious uveitis in 2016[8] recommends the following stopping criteria: patients who respond and achieve drug induced disease remission will continue therapy for up to 2 years. After 2 years, funding for therapy will be withdrawn. If there is disease relapse, consideration to restarting adalimumab therapy will be given.

Moreover, AbbVie have consulted various external experts in uveitis. As shown in Table 3, the vast majority propose at least 1 year of quiescence, if not 2 years, before attempting to withdraw adalimumab, with a few opting for indefinite therapy. These recommendations are also supported in the literature by Jabs et al[9].

Table 3: Expert opinions on long-term adalimumab treatment

- After 2 years of no activity, prolong duration between treatments
- After 12 – 18 months of therapy, stop if disease is inactive.
- Indefinitely if no side effects.
- After 2 years and no activity. Unable to wean in children but successful in older patients
- After 2 years of quiescence
- Depends on disease and subject risk/history (3 years to indefinitely)
- At least 1 year after remission
- Consider gradual tapering after 6 months of inactivity
- Start tapering over 18 – 24 months (12 months minimum). Account for disease status and side effects and complications
- Taper every 2 weeks for 6 months, every 3 weeks for 6 months, every 4 weeks for 6 months, every 8 weeks for 6 months.
- At least 1 – 2 years of remission. Account for etiology, severity, specific patient history

* [redacted]

Finally, a clinical commissioning policy published by NHS England looking at infliximab (Remicade) and adalimumab (Humira) as anti-TNF treatment options for adult patients with severe refractory uveitis undertook a retrospective study of data from a multicentre ocular inflammation biologics registry which included patients capturing routine clinical therapy and disease states in uveitis within the UK. Adult patients receiving either adalimumab (40 mg every other week week) or infliximab (3-5 mg/kg every other week) were included. This analysis concluded that all patients (n=41) on biologics showed clinical remission after a mean (± SD) follow-up of 1.36(± 0.88) person years[10].

Proposed amendment: AbbVie believe that for most patients in quiescence, stopping treatment after 2 years is a reasonable assumption and should be included in the base case analysis rather than a separate explanatory analysis.

Possible likely impact on ICER: Using a discontinuation rule at 2 years, the ICER for active uveitis decreases to £35,299 while the ICER for inactive uveitis decreases to £84,132.

Issue 3. Mapping VFQ-25 to EQ-5D

Description of the issue: The Assessment Group have derived utilities for their economic model using two different approaches for adalimumab and dexamethasone. For adalimumab they have taken directly assessed EQ-5D utilities from the VISUAL I and VISUAL II studies. For dexamethasone, in the absence of on-treatment EQ-5D measurements, they have mapped scores from the VFQ-25 questionnaire, based on a linear regression estimate derived from baseline data from the HURON study.

AbbVie would like to express their concerns regarding this approach, as directly assessed EQ-5D utilities are relatively insensitive to visual impairment, which may impact on the validity of consequent cost utility models[11]. VFQ-25, by contrast, is explicitly designed to measure the dimensions of self-reported vision-targeted health status that are most important for persons who have chronic eye diseases[12]. Therefore, by using different instruments for assessing utility benefits in the two arms of the model, the risk exists that non-comparable results will be obtained. Awareness of the potential limitations of EQ-5D as a means to accurately estimate utility in certain clinical conditions and the need to assess utility in a consistent fashion within a model are both explicitly acknowledged by NICE in their Guide to the methods of technology appraisal[13].

Specifically, it might be anticipated that patients with significant visual impairment will have their impaired quality of life captured more effectively using the VFQ-25 mapped utility, compared with the generic estimate obtained using the EQ-5D. In this circumstance, the incremental utility gains associated with any given improvement in vision would therefore be expected to be greater for the VFQ-25-assessed patient than for the EQ-5D-assessed patient.

In order to explore whether this concern is justified, we accessed individual patient data from both VISUAL I (patients with active disease) and VISUAL II (patients with inactive disease). In these studies, both VFQ-25 and EQ-5D were administered throughout the studies, allowing both the direct and mapped estimates of utility to be calculated for each patient at all time points. To convert VFQ-25 results to utilities, we used the same mapping formula developed by the Assessment Group for the dexamethasone arm of their model:

*EQ-5D utility = 0.4454059 + (VFQ-25 score * 0.0051322).*

The direct EQ-5D estimates were derived from the EuroQol-defined utility index for EQ-5D, as currently used by the Assessment Group in the adalimumab arm of their model.

<u>VISUAL I</u>

In patients with active disease, the mean directly measured baseline utility in adalimumab-treated patients was [redacted]. The VFQ-25 mapped estimate of utility was [redacted], equating to a mean difference of [redacted]. Figure 1 below shows the comparison of the two measures over time, while Table 4 shows the comparative incremental utility versus baseline over selected time points in the study.

This analysis shows that the direct EQ-5D response is flatter than the VFQ-25 mapped estimate, starting from a higher baseline and showing a lesser response to treatment in the first year of treatment. From week 40 onward, the estimates are comparable. The net effect on the incremental utility vs baseline is considerable, with the VFQ-25 mapped estimate yielding larger increments throughout the study.

Figure 1: Comparative point estimates of utility at all time points in the VISUAL II study (adalimumab-treated patients)

Table 4: Comparative incremental utility vs baseline at key time points in the VISUAL I study (adalimumab-treated patients)

Time point	Utility		Incremental utility vs baseline	
	Direct (EQ-5D)	Mapped (VQ-25)	Direct	Mapped
Baseline	[redacted]	[redacted]	-	-
20 weeks	[redacted]	[redacted]	[redacted]	[redacted]
40 weeks	[redacted]	[redacted]	[redacted]	[redacted]
60 weeks	[redacted]	[redacted]	[redacted]	[redacted]
80 weeks	[redacted]	[redacted]	[redacted]	[redacted]

VISUAL II

In VISUAL II, the same qualitative pattern is seen as in VISUAL I, although owing to the inactive nature of their disease, differences both at baseline and on treatment are attenuated. The mean directly measured baseline utility in adalimumab-treated patients was [redacted], while the VFQ-25 mapped estimate of utility was [redacted], equating to a mean difference of [redacted]. Figure 2 below shows the comparison of the two measures over time, while Table 5 shows the comparative incremental utility versus baseline over selected time points in the study.

Figure 2: Comparative point estimates of utility at all time points in the VISUAL II study (adalimumab-treated patients)

Table 5: Comparative incremental utility vs baseline at key time points in the VISUAL II study (adalimumab-treated patients)

Time point	Utility		Incremental utility vs baseline	
	Direct (EQ-5D)	Mapped (VQ-25)	Direct	Mapped
Baseline	[redacted]	[redacted]	-	-
20 weeks	[redacted]	[redacted]	[redacted]	[redacted]
40 weeks	[redacted]	[redacted]	[redacted]	[redacted]
60 weeks	[redacted]	[redacted]	[redacted]	[redacted]
80 weeks	[redacted]	[redacted]	[redacted]	[redacted]

Proposed amendment: In order to ensure that the assessment of incremental cost effectiveness is a true representation of the relative performance of the two treatments, AbbVie propose that VFQ-25 mapped estimates of utility should be used for both treatment arms in the base case analysis, with direct EQ-5D derived values being presented as a scenario analysis.

Possible likely impact on ICER: The analysis above confirms that the approach used to derive utility estimates for dexamethasone (VFQ-25 mapping) is more sensitive to the quality of life impact of changes in visual impairment than the directly estimated utilities used for adalimumab, resulting in clinically significant differences in estimated incremental utilities. This would lead to improvements in QALY gained and a corresponding improvement in the ICER. This effect is particularly pronounced in patients with active uveitis. In patients with inactive disease, the difference between the approaches is considerably less.

Issue 4. Mapping VFQ-25 to EQ-5D (continued)

Description of the issue: AbbVie require clarification on method of deriving utility values using the HURON IPD data only and raise several further issues:

(1) We appreciate that the AG did not have the VFQ-25 IPD from the VISUAL I and VISUAL II trials at the time of development. [redacted]

(2) The model allows a selection for the source of utilities for adalimumab vs. placebo (directly measured EQ-5D or mapped from VFQ-25) but for the comparison of dexamethasone vs. placebo the only available source of utilities are the mapped VFQ-25 estimates (using VFQ-25 data captured at each time point in the trial mapped onto EQ-5D).

Proposed amendment: The proposed amendments are addressed in order that the issues were raised above.

(1) A mapping algorithm using the VISUAL trial data should be developed. Furthermore, analyses should be run using the VISUAL trial IPD established mapping algorithms and included in the model.
(2) As there is directly derived EQ-5D data from the HURON trial, the option should be present to select utilities from directly measured EQ-5D for dexamethasone vs. placebo.

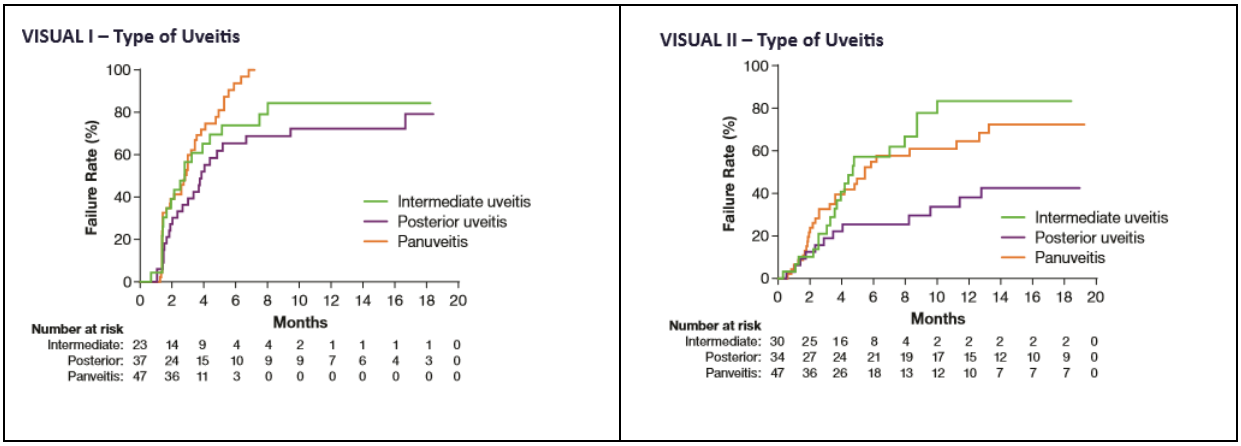
Possible likely impact on ICER: The impact on the ICER is unknown and would depend on the extent to which the QALYs/incremental QALYs are impacted.

Issue 5. Patients with pan-uveitis are not included as an important subgroup

Description of the issue: Identification of important subgroups (page 25); patients with pan-uveitis are an important subgroup since these patients have the highest risk of unmanageable disease (recurrent or persistent inflammation) compared to intermediate and posterior uveitis[14] and are at the highest risk of vision loss[3]. A recent UK retrospective study by Jones et al 2015[15] indicated that 21.1% of uveitis patients have pan-uveitis. Uveitis patients with active disease are at higher risk than those with inactive disease.

An analysis of the placebo arms (intention to treat sets) from VISUAL I and VISUAL II was presented at the American Academy of Ophthalmology Annual meeting in 2016[14]. A proportional hazards regression with backward elimination was used to determine prognostic baseline demographic factors. A higher risk of recurrent or persistent inflammation (defined as treatment failure, the primary end-point of the VISUAL clinical trials) was associated with pan-uveitis in both VISUAL I and VISUAL II studies. In VISUAL I, the HR for recurrent or persistent inflammation in patients with intermediate versus pan-uveitis was 0.63 (0.36-1.11) and the HR for posterior versus pan-uveitis was 0.46 (0.27-0.79), p=0.015. In VISUAL II, the HRs were 0.97 (0.53-1.78) and 0.38 (0.19-0.76) respectively, p=0.016. In VISUAL II, male gender, three or more flares in the last 12 months and >20 mg corticosteroid dose at baseline were also significantly associated with a higher risk of recurrence.

Figure 3: Kaplan Meier curves for recurrent or persistent inflammation (defined as treatment failure, the primary end-point) for the placebo arms of VISUAL I and VISUAL II[14].



A retrospective review of medical records of 315 consecutive patients attending a tertiary referral uveitis service at the Birmingham and Midland Eye Centre over a 2 year period (January 1998 to December 2000) by Durrani et al revealed that patients with pan-uveitis were most likely to experience visual loss (125/148 patients, 84.5%) compared with 7/11 (63.6%) of patients with posterior disease and 17/33 (51.5%) of those with intermediate disease. Over half of patients with pan-uveitis or posterior uveitis had severe visual loss (≤6/60): 53% and 57% respectively[3].

In VISUAL I, the mean ± SD duration of uveitis was 46±63 months and most patients (91%) had bilateral disease. Pan-uveitis was the most common form (45%, n=97), followed by posterior uveitis (33%, n=73) and intermediate uveitis (22%, n=47)[16].

Subgroup data on the intention to treat pan-uveitis population is available in the clinical study report for VISUAL I[5] (Figure 4 and Figure 5). There was a statistically significant reduction in time to treatment failure with adalimumab versus placebo in patients with pan-uveitis, [redacted], median time to failure was [redacted] months with adalimumab versus [redacted] months with placebo [page 1668] (compared with 5.6 months and 3 months in the total population)[16]. The HR for the primary end-point in patients with pan-uveitis was [redacted] [5] versus 0.5 (95% CI: 0.36-0.70) in the total study population (all types)[16].

Figure 4: Time to treatment failure in VISUAL I – pan-uveitis subgroup (n=97)[5].

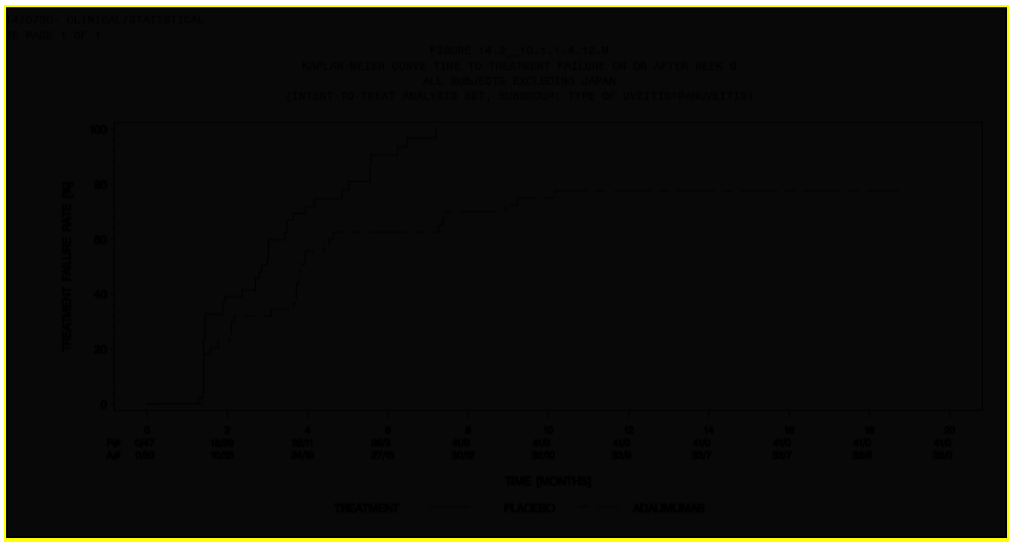


Figure 5: HR of time to treatment failure by type of uveitis (VISUAL I)[5].

Proposed amendment: Since pan-uveitis patients are clearly one of the subgroups that is associated with a high risk of vision loss, Abbvie recommend to include patients with active pan-uveitis as an exploratory analysis.

Possible likely impact on ICER: Patients at highest risk of visual loss are more likely to benefit from treatment than those at lower risk and therefore treatments are more likely to be cost-effective in the high-risk subgroup of patients with pan-uveitis.

Issue 6. The impact of vision loss (rather than blindness) on utility and costs is not included

Description of the issue: The model includes the impact of blindness on utility and costs but it does not incorporate the impact of vision loss on utility and costs. In the current model developed by the Assessment Group, utility and costs are not explicitly linked to vision loss and disutilities as well as the associated cost are only applied when patients become blind. NICE has previously concluded that the utility associated with different levels of visual acuity is applicable across vision disorders, and the paper by Czoski-Murray et al 2009[18] was recommended by a previous NICE Evidence Review Group for valuing visual acuity health states[19]. In this paper, the authors estimated a linear relationship between Best Seeing Eye visual acuity (logMAR) and Time Trade Off (TTO) utility.

TTO utility=0.828-0.359(logMAR)

In the Durrani et al 2004[3] paper, the rate of moderate vision loss (between 0.48 and 1 logmar) at 3.07 years was 10/315 patients. Thus, in these patients, the utility decrement would be 0.359*0.48=~0.17

The model includes the impact of blindness on costs but it does not incorporate the impact of vision loss on costs, nor does the model recognize that the cost of uveitis may depend on the visual acuity.

Proposed amendment: Incorporate the impact of vision loss on utility and costs into the model.

Possible likely impact on ICER: This would lead to an improvement in QALY gained and a corresponding improvement in the ICER.

Issue 7. Age at start of the model

Description of the issue: The model has used the age at start from the HURON trial taking the average age 44.8 (Table 4 of the assessment report, section 6.2.1.1). The adalimumab trials have not been considered here. Page 110 of the assessment report states: *The time horizon of the model is the lifetime of patients (up to age 100 years) and a starting age of 44 years was used, representing the average age of patients with non-infectious posterior segment-involving uveitis across the HURON and VISUAL trials* This statement is misleading as this average age is only correct for the HURON trial.

Proposed amendment: AbbVie suggest re-running the base case for comparisons involving adalimumab using the average age at start from the VISUAL I and VISUAL II trials listed in Table 4 of the assessment report as 42.7 years and 42.5 years, respectively.

Possible likely impact on ICER: Using the mean age at study entry into the VISUAL trials, rather than the mean age from HURON, will reduce the ICER.

Issue 8. Impact of disease flares on vision loss is not included in the model

Description of the issue: The cumulative impact of flares is not considered in the Assessment Group model and so the model underestimates the benefits of adalimumab. Post-hoc analyses from VISUAL I and VISUAL II reveal that adalimumab reduces the rates of flares during the time a patient is on therapy[20]. If a patient stops adalimumab, it is assumed in the current model that the patient will immediately return to baseline utility (and vision) without any long-term effects. However, permanent vision loss may be associated with severe flares. Post-hoc analyses of the VISUAL I and VISUAL II trials demonstrate that each flare marked by either deterioration of 1 grade vitreous haze, anterior chamber cell grade and occurrence of lesions can lead to substantial loss of visual acuity[20].

Proposed amendment: Inclusion of the impact of disease flares on vision loss within the model.

Possible likely impact on ICER: Small prevention of visual acuity loss carried over long period of time could impact on the estimate of QALYs over time and could lead to a reduction of the ICER.

Issue 9. Exclusion of costs of optical correction by spectacles post-cataract surgery for steroid-related cataract formation

Description of the issue: There is an assumption from clinical advisors that cataract surgery (for steroid-related cataract formation) is relatively safe and efficacious (background Section 3). We agree that cataract surgery is commonly and successfully performed in the UK. It should be noted that after implantation of the intraocular lens during cataract surgery the patient has a fixed focal point (usually to obtain optimal distance vision, and thus leading to a requirement for near correction with spectacles)

Proposed amendment: Optical correction (typically to correct for near vision) by spectacles is a very common outcome of cataract surgery for steroid-related cataract formation. The additional expense of optical correction should be included into the cost-effectiveness modelling.

Possible likely impact on ICER: ICER for steroid treatments will be increased.

Issue 10. Exclusion of indirect cost of blindness in the model

Description of the issue: Currently in the model the cost of blindness includes only direct costs and excludes indirect costs, in line with the scope. However, the indirect cost of blindness is substantial and falls on society. These costs can last a lifetime and accumulate to large sums. This is an element that is unique to blindness and is not found in other conditions. A recent study by Green et al 2016[21] showed that the estimated indirect cost of blindness in the Republic of Ireland was €20,643 (i.e. £17,684) per patient per year, of which the majority was indirect costs.

The impact of the indirect costs of blindness are acknowledged in the Assessment Group report – page 165 *non-infectious uveitis affects a working-age population and can reduce workplace productivity. In addition, the disease can affect leisure time. Therefore, there are likely to be additional non NHS and PSS costs and benefits of the interventions not captured within our analyses.*

Proposed amendment: Include indirect costs within the model as an explanatory analysis

Possible likely impact on ICER: AbbVie have estimated that including the indirect cost of blindness at £17,684 in the model, the ICER for active uveitis decreases to £69,331 while the ICER for inactive uveitis decreases to £272,263 in the current base case. When the Durani et al[3] rate of visual loss is used, the cost per QALY become dominant in active disease and £34,849 in inactive disease

Issue 11. Limited literature review

Description of the issue: The Assessment Group report includes a limited literature review within a narrow therapeutic area in the suggested date limits. A number of key research articles are on the horizon, as the author has described on page 79, including VISUAL III. VISUAL III is a non-randomised extension study of the VISUAL I and VISUAL II studies and will provide data on longer term data on the efficacy and safety of adalimumab.

Proposed amendment: NICE should be aware that VISUAL III is due to report in July 2017.

Possible likely impact on ICER: Reduced uncertainty around long-term extrapolation and improved reliability of ICER.

Clarifications and corrections

AbbVie have identified a number of occasions within the Assessment Group report where further clarification can be provided or factual inaccuracies corrected, as detailed in the Table 6. AbbVie request that any inaccuracies in reporting within the Assessment Group report be amended, as suggested in the final column of the table.

Table 6: Minor clarifications and corrections

Section of the report	Description of the issue	Suggested change and justification of the amendment
The use of the terminology 'limited current practice'	The control arms from each trial (HURON, VISUAL I and VISUAL II) are described in the assessment report as limited current practice. This term is accompanied by denotation of which trial the limited current practice is referring to. However, using the same terminology is considered to be misleading to the reader as, in fact, the control arms in the HURON trial vs. the VISUAL trials are substantially different	AbbVie propose amending the term limited current practice to placebo, in order to avoid confusion
Page 6 and page 110-111	The AG report states that the de novo Markov model includes five health states: (i) treatment: no permanent blindness; (ii) treatment failure: no permanent blindness; (iii) permanent blindness; (iv) remission; and (v) death. In the Markov trace, however, the health states are (1) inconsistent with that stated in the report and (2) inconsistent between arms. Specific examples include the following: • In the dexamethasone vs sham trace there are three health states: Reduced sight, blindness, and death. • In the dexamethasone vs systemic steroids & Immunosuppressants trace there are three health states: On treatment, blind, and death • In the adalimumab vs systemic steroids & immunosuppressants trace the adalimumab arm follows the 5 state structure whereas the systemic steroids & immunosuppressants follow	Health states should be consistently implemented and labelled across model arms. Alternatively, the AG report description of the health states should be updated to accurately reflect what is modelled.

	the 3 state structure	
Impact of health problem (page 17) and significance for the NHS (page 18)	The burden of disease is not fully quantified. Impact of the health problem mentions that AEs associated with immunosuppressants can lead to substantial reductions in HRQOL. However, data is available which shows that patients with intermediate, posterior and pan-uveitis have poorer HRQOL compared with the general population and that visual impairment is a key factor in influencing HRQOL[22-25]. A post hoc analysis of HRQOL and patient reported outcomes (PRO) in patients with non-infectious intermediate or posterior uveitis participating in the HURON trial reports that QOL was significantly impaired in patients with uveitis when compared with the US general population ($p<0.001$)[24]. Significance for the NHS does not mention the financial impact of the complications of uveitis. Studies have demonstrated that healthcare and indirect (work loss/leaving the workforce) resource use and costs are significantly increased in patients with non-infectious intermediate, posterior and pan-uveitis compared with the general population[26,27]. Patients with vision loss resulting from their disease have even higher healthcare costs[28].	Inclusion of studies detailed in Section 2.1.3 Impact of disease in the AbbVie submission.
Section 3.3, page 23	Adalimumab is administered as a subcutaneous injection containing 40 mg preparation of the active drug.	Would be clearer to explain the dosage regimen here The recommended dose of adalimumab for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting 1 week after the initial dose.
Table 4, page 36	Information is missing on the number of patients from the UK in VISUAL I	[redacted] patients were enrolled in the UK (see Table 14.1_1.1 page 528 of the CSR)[5]

Table 4, page 36	Information is incorrect on the number of sites in VISUAL II	62 sites (see page 2 of published paper[29])
Page 45, paragraph 2	It is stated "priori sample size calculations for detecting between group differences for the specified primary outcomes at a significance level of 5% indicated that 234 patients were needed to achieve a power of 90% in VISUAL I;" Information is incorrect on the number of patients needed to achieve a power of 90%. There seems to be a misinterpretation of the sample size calculation in the protocol and the number of events. The CSR of VISUAL I[5], page 355, and the EPAR state that "For conservative purposes, it is assumed that failures will begin to occur after 2 months of study duration as the prednisone taper reaches lower doses. In addition, a pooled dropout rate of 35% over 12 months has been assumed. Using these failure rate assumptions for a log-rank test and a two-sided significance level of 5%, a total of 138 events are needed. The assumptions also include the following: • a power of 90%, • an average accrual rate of 4 subjects per month in the first 30 months and 7 subjects per month thereafter"	This statement should read "138 patients were needed to achieve a power of 90% in VISUAL I"
Table 7, page 46	Table 7 indicates that VISUAL I trial is not adequately controlled introducing a high risk of bias. AbbVie wish to highlight that based on the information in the point above (i.e. number of patients needed to achieve a power of 90%) VISUAL I is of adequate control	"Y" for VISUAL I, 4th quality assessment item
Page 67	Macular oedema VISUAL studies (page 67); do not mention pre-specified post hoc analyses of macular oedema in patients without macular hole and/or retinal detachment in VISUAL I. These analyses demonstrated that adalimumab did confer significant benefit over placebo in patients	Include data on pre-specified post hoc analyses of macular oedema in patients without macular hole and/or retinal detachment in VISUAL I, which can be found in Table 13 of the AbbVie

	without macular hole and/or retinal detachment in VISUAL I.	submission.
Clinical section	VISUAL I and VISUAL II provide evidence for adalimumab in non-infectious intermediate, posterior and pan-uveitis. However, additional evidence is available from a retrospective audit of 41 patients in the UK on biologics.	Include data on the retrospective audit of 41 patients in the UK on biologics, which can be found on page 46 of the AbbVie submission (copy below). The Clinical Commissioning Policy for anti-TNF treatment options for adult patients with severe refractory uveitis contains details of a retrospective audit of data from a multicentre ocular inflammation biologics registry which captured routine clinical data in uveitis within the UK. Patients >18 years who received either adalimumab (40 mg every other week) or infliximab (3-5 mg/kg every 2 weeks) were included in the audit. All patients (n=41) on biologics showed clinical remission after a mean (± SD) follow-up of 1.36 (± 0.88) person years. More patients had an improvement in visual acuity than had worsening of visual acuity (48.8% versus 17.1%). Steroid dose was reduced to <10 mg prednisone in the majority of patients (88.9%) and almost half of patients (45.2%) stopped steroid use altogether. There was also a reduction in the use of immunosuppressants; 83.33% of patients on biologics had a reduction in the number and/or use of immunosuppressants.
Table 27, page 99	The clinical justification for not undertaking an indirect comparison is sensible; however, AbbVie would like to clarify why the AG initially considered an indirect comparison for the VFQ-25 outcome. In table 27 of the assessment report there are no values reported for the VFQ-25 composite score (change) for the	AbbVie propose that more clarification around the VFQ-25 composite score (change) from the HURON trial be included in the report. If this issue is caused by an error in reported values then AbbVie suggest correction to the

	DEX 700 arms of the HURON trial, making it difficult to understand why this outcome was initially considered for a potential indirect comparison. Furthermore, AbbVie would like clarification on how p values for the non-reported VFQ-25 composite score (change) were estimated.	assessment report be made.
Table 32, page 118 probability of AEs per cycle	The probability of fracture and diabetes for adalimumab, LCP(VI), and LCP(VII) in Table 32 are inconsistent with the probabilities used in the model (Excel tab: "CT, AEs & RT").	AbbVie wish this discrepancy to be addressed and the correct numbers to be reported
Page 124, regression equation	The assessment report outlines a regression equation reported by Ara and Brazier that was used to estimate the age related utility that is applied in the model. The formula includes coefficients A, B and C as listed below: A = -0.0001728, B = -0.000034, C = 0.9584588 However, these coefficient values do not match those in the AG model. The parameter values are instead applied as: MaleCoefficient= 0.0212126 AgeCoefficient= -0.0002587 Age2Coefficient= -0.0000332.	AbbVie would like clarification on why the two sets of coefficients differ.
Table 67, page 217 and Table 68, page 218	The total QALYs, total costs, incremental QALYs, incremental costs and ICER in Table 67 (breakdown of the deterministic base case results for active population) and Table 68 (breakdown of the deterministic base case results for inactive population) do not match with the corresponding values in Table 48 (deterministic base case results for active population) and Table 58 (deterministic base case results for inactive population), respectively.	This discrepancy to be addressed and the correct numbers to be reported
Deterministic sensitivity analysis, "DSA" tab, cell B15	Raised IOP is listed as a parameter to be tested in one way sensitivity analysis (OWSA) (cell B15 in the DSA tab). When varying base case values in the OWSA, the expectation is to vary parameters (for high and low values) without	AbbVie would like clarification for the rationale of dividing by 2 and multiplying by 2 to obtain the high and low values in the DSA.

	confidence intervals by a consistent percentage. The raised IOP mean value has been divided by 2 to estimate the low value and multiplied by 2 to estimate the high value.	AbbVie also propose using the conventional percentage variation.
Probabilistic distributions used for cost inputs in the AG model, “other” tab, row 28-41	The expected distribution to be applied to cost inputs is gamma and log normal. Where costs are considered in probabilistic sensitivity analysis, the gamma distribution has been applied. This is consistently the case in the cost tab. However, costs considered in the other inputs tab list NHS reference costs (row 28-41) and instead apply a normal distribution.	AbbVie would like clarification for the use of the normal distribution around cost inputs on the other inputs tab as mentioned in the description of the problem.

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Allergan comments on the assessment report prepared for the NICE appraisal of dexamethasone intravitreal implant and adalimumab for the treatment of non-infectious uveitis [ID 763]

Submitted on: 25 January 2017

Executive Summary

- The assessment group (AG) model indicates that the risk of blindness in the comparator group is one of the key drivers of ICER estimates. Allergan considers that the risk of blindness for the posterior segment uveitis target population would be somewhere between the estimates provided from all patients in the Dick et al. (2016) population and the tertiary referral population in Durrani et al. (2004). Therefore, the ICER for DEX 700 vs standard care is likely to be lower than the £20,058 base case deterministic estimate.
- The AG model shows that the ICER estimates for DEX 700 are highly sensitive to the relative risk of blindness for DEX 700 vs standard care. In the base case DEX 700 was modelled as reducing the risk of blindness vs standard care with a relative risk (RR) of 0.5 applying for 30 weeks then reverting to 1 after this period. It is argued that a reduced risk of blindness would be expected for patients beyond 30 weeks after each DEX 700 implantation. The rationale for DEX 700 having a longer-term impact on blindness is based on the ability of DEX 700 to reduce irreversible damage by controlling macular oedema.
- The AG model assumes that the duration of treatment effect of a single DEX 700 implant is 30 weeks for all patients in the base case. Utility and risk of blindness returns to baseline instantly after 30 weeks. Observational evidence indicates that the duration of treatment effect varies by patient. Data from a retrospective study conducted by Tomkins-Netzer et al. (2014) indicated that the median time to relapse for patients receiving DEX 700 was six months for the first implant but this ranged from two to 42 months and the overall relapse rate was only 69%. Data from a retrospective study conducted by Zarranz-Ventura et al. (2014) observed a median time to repeat implantation for patients receiving DEX 700 of 10 months (95% CI: 6.3 to 13.6 months). These data indicate that some patients will be controlled on DEX 700 for a longer period than 30 weeks and these benefits are not captured in the base case using a fixed treatment effect duration of 30 weeks for all patients. Sensitivity analyses presented in the AG report indicate that increasing the duration of treatment effect for DEX 700 beyond 30 weeks reduces the ICER markedly below the £20,058 estimate for the base case.
- The AG model does not include the impact of malignancies for patients receiving standard care despite this being a risk for patients receiving long-term immunosuppressants. Yates et al. (2015) found that among patients treated with systemic immunosuppressants vs corticosteroids only, an additional 1.67 malignancies would be observed per 100 person-years. The avoidance of systemic adverse events is one of the key reasons why DEX 700 may be preferred over long-term systemic immunosuppressant therapy and it is argued that the immunosuppressant-sparing benefits of DEX 700 therapy have not been fully captured within the current cost and QALY estimates.
- DEX 700 is an innovative implant form of dexamethasone and adalimumab is currently the only alternative licensed treatment for posterior segment uveitis. Therefore, given the innovative nature of the technology and the acknowledgement that estimating the long-term benefits of treatment are uncertain, but that there is a significant risk of blindness for poorly controlled patients with posterior segment uveitis, Allergan considers that DEX 700 should be recommended by NICE for this indication.
- The AG report notes that it is challenging to model the cost effectiveness of DEX 700 for bilateral disease given that the available data from HURON was based on treatment of one eye only. However, Allergan considers it would be inappropriate to restrict access to treatment of only one

eye for patients with bilateral disease because of uncertainty over the magnitude of the ICER. If neither dexamethasone nor adalimumab are recommended for patients with bilateral disease, this would lead to patients with the highest risk of incurring disability due to vision loss being left with no licensed treatment option.

- The AG report acknowledges that there are likely to be additional non-NHS and PSS costs and benefits which are not captured in the model. Given the working age population affected by posterior segment uveitis, the detrimental impact of the condition on work productivity and the societal costs associated with blindness, Allergan considers that substantial non-NHS costs and benefits will be excluded from the AG model. These non-NHS and PSS costs and benefits provide a further rationale for the recommendation by NICE of DEX 700 for this indication.

Allergan welcomes the opportunity to comment on the assessment report prepared for the appraisal of dexamethasone intravitreal implant (hereafter referred to as DEX 700) for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

The following comments are arranged around key points regarding the clinical and cost-effectiveness of DEX 700. ICER estimates are presented using the deterministic analyses from the assessment group (AG) model. Probabilistic ICERs are not presented given the similarity between the observed probabilistic and deterministic estimates for DEX 700.

1 Risk of blindness for patients receiving standard care

The AG model indicates that the risk of blindness in the comparator group is one of the key drivers of ICER estimates. The base case estimates for blindness on standard care were based on data from a US study by Dick et al. (2016); 6.6% of patients with uveitis were legally blind after 10 years in the absence of death from other causes (1). Estimates from studies by Tomkins-Netzer et al. (2014) and Durrani et al. (2004) were considered in sensitivity analyses, giving lower and higher estimated risks of blindness, respectively (3, 4). The risk of blindness from Tomkins-Netzer (2014) gives an ICER of £28,089 for DEX 700 vs LCP-H and the risk of blindness from Durrani (2004) gives an ICER of £557 for DEX 700 (assuming a relative risk of blindness of 0.5 vs LCP-H as per the AG model base case). The AG report notes that the estimate by Tomkins-Netzer (2014) was considered by a clinical expert (Alastair Denniston) to be an underestimation of the risk in the modelled population because it was taken from a cohort of patients including anterior and infectious uveitis. Therefore, if the estimate from Tomkins-Netzer (2014) is an underestimate of the risk of blindness for the population with posterior segment uveitis, the ICER for DEX is likely to be significantly lower than the £28,089 upper estimate.

Using data from Durrani (2004) was considered to provide an overestimation of the risk of blindness for patients with posterior segment uveitis receiving standard care in the model because this population was drawn from a tertiary referral clinic. Conversely, the estimates of risk based on data from Dick (2016) were based on the risk from the date of diagnosis to year 10 for all patients with a diagnosis of non-infectious posterior segment uveitis. These estimates include patients with a range of disease severity including patients well-controlled on first line therapy. Patients receiving DEX 700 are expected to have failed first line systemic corticosteroid therapy. It is therefore considered that the risk of blindness would be somewhere between the estimates provided for all patients from Dick (2016) and the tertiary referral population from Durrani (2004). Therefore, the ICER for DEX 700 vs LCP-H is likely to be lower than the £20,058 base case deterministic estimate.

2 Relative risk of blindness for patients receiving DEX 700 therapy

The AG model shows that the cost-effectiveness estimates for DEX 700 are highly sensitive to the relative risk of blindness for DEX 700 vs LCP-H. In the base case DEX 700 was modelled as reducing the risk of blindness vs standard care with a relative risk (RR) of 0.5 applying for 30 weeks then reverting to 1 after this period. Assuming an RR of 1 (no effect of DEX 700 in reducing blindness) results in a deterministic ICER for DEX 700 vs LCP-H of £50,627. Assuming a RR of 0 (no blindness while on DEX 700 for 30 weeks) results in an ICER of £8,688. It is argued that a reduced risk of blindness would be

expected for patients beyond 30 weeks after each implantation because DEX 700 reduces irreversible damage by controlling macular oedema. It is argued that this would have a lasting impact on the risk of blindness beyond the 30-week period.

3 Duration of treatment effect on HRQoL for DEX 700

The AG model base case assumes that the treatment effect of a single DEX 700 implant is 30 weeks for all patients. Utility returns to baseline after 30 week because the HURON trial ran for 26 weeks then an assumption that utility would return to baseline four weeks later. The risk of blindness also returns to that of standard care instantly at the 30 week timepoint. Sensitivity analyses conducted using the model indicate that increasing the duration of treatment effect for DEX 700 reduces the ICER markedly as shown in table 45 from the AG report:

Table 45: Results of exploratory analyses with varying duration of treatment effect on HRQoL (deterministic)

	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER
LCP(H)	14.613	£39,655			
Dex:26 weeks	14.637	£40,256	0.024	£600	£24,715
Dex:30 weeks*	14.641	£40,235	0.029	£580	£20,058
Dex:34 weeks	14.646	£40,214	0.033	£559	£16,692
Dex:42 weeks	14.655	£40,173	0.043	£518	£12,154

*base case

Observational evidence indicates that the duration of treatment effect varies by patient. In the AG model, it appears that the duration of treatment effect for DEX 700 is fixed for all patients at 30 weeks. Data from a retrospective study of patients at Moorfields hospital, London, conducted by Tomkins-Netzer et al. (2014) indicated that the median time to relapse for patients receiving DEX 700 was six months for the first implant but this ranged from two to 42 months and the overall relapse rate was only 69% (2). Relapse was defined as the first follow-up with foveal thickening, doubling of the angle of BCVA because of a vitreous haze score of more than 0, or both, compared with the best result after treatment. Foveal thickening was determined as CRT of more than the average best CRT plus 1 standard deviation. Data from a retrospective study conducted by Zarranz-Ventura et al. (2014) observed a median time to repeat injection for patients receiving DEX 700 of 10 months (95% CI: 6.3 to 13.6 months) (5). A post authorisation observational safety study conducted by Allergan found a mean time between injections of DEX 700 of 37 weeks [SD 18 weeks; median 31 weeks] for patients with posterior segment uveitis (6). This mean estimate does not take account of any patients who achieved long-term control using only one injection. The range of time to repeat injections (15 to 106 weeks) indicates that this time period varies and that patient time to repeat injections are not distributed symmetrically. These data indicate that some patients will be controlled on DEX 700 for a longer period than 30 weeks and these benefits are not captured in the base case using a fixed treatment effect duration of 30 weeks for all patients.

In conclusion, it is reasonable to assume that DEX 700 can increase patient HRQoL beyond 30 weeks per implant and therefore that the ICER for DEX 700 is likely to be lower than the £20,058 estimate from the deterministic base case.

4 Modelling of adverse events for standard care

The AG model does not include malignancies for patients receiving standard care despite this being a risk for patients receiving long-term immunosuppressants. The development of malignancies is expected to have a significant impact both in terms of costs and utility decrement.

Yates et al. (2015) conducted a retrospective cohort study of 132 patients treated for ≥ 6 months with systemic immunosuppressant therapy and 58 patients treated with systemic corticosteroids only for uveitis (7). Twenty-five malignancies were observed in 17 patients during a median follow-up of 7.34 years, equivalent to 2.10 per 100 person-years in the immunosuppressant group and 0.43 per 100 person-years in the corticosteroid-only group. The most common malignancies were non-melanoma skin cancers and non-Hodgkin's lymphoma. Compared with the corticosteroid treatment-only group, the immunosuppressant group was at an increased risk of any malignancy (adjusted HR 4.36; 95% CI 1.02–18.7). No cancer-related deaths occurred in the study. This study indicates that, among patients treated with systemic immunosuppressants, an additional 1.67 malignancies would be observed per 100 person-years. Costs would be expected to be high for the treatment of non-Hodgkin's lymphoma.

The calculation of utility decrement via mapping from VFQ-25 scores is unlikely to fully capture the impact of non-visual AEs such as malignancy because only one question in the VFQ-25 relates to general health. Since no malignancies were observed in the Sham or DEX 700 arms within the 26-week study period of the HURON trial, it is not possible to assess how they would be related to VFQ-25 scores. However, it is argued that the utility of patients on standard care is likely to be overestimated in the AG model given the expected incidence of malignancies for patients on long-term immunosuppressant therapy. The avoidance of systemic adverse events is one of the key reasons why DEX 700 may be preferred over long-term systemic immunosuppressant therapy and it is argued that this benefit has not been fully captured in either the cost or QALY estimates presented in the AG report.

5 Immunosuppressant-sparing effect of DEX 700

The AG report notes that if "*dexamethasone or adalimumab led to a reduction in the use of immunosuppressants and/or corticosteroids without this impacting upon efficacy in these treatment groups, then they would be more cost-effective than currently predicted*."

The retrospective study by Zarranz-Ventura (2014) found that the probability of a dose reduction of corticosteroids or immunosuppressant therapy for patients receiving DEX 700 was 36% at 1 month, 42% at 3 months, 46% at 6 months, and 62% at 12 months (5). In this study dose reduction was defined as ≥ 5 mg of prednisolone or any decrease in second-line immunosuppressant therapy dose for patients on systemic treatment at baseline. The AG report notes that in the HURON RCT only one patient (1.3%) receiving DEX 700 started immunosuppressant therapy after baseline compared to eight patients (10.5%) receiving Sham. These data suggest that DEX 700 will reduce the need for long-term immunosuppressant therapy. Therefore, Allergan considers that DEX 700 would be more cost-effective than currently predicted, particularly if AEs associated with malignancy because of long-term immunosuppressant use were also to be included, as outlined in section 4 above. The

immunosuppressant-sparing benefits of DEX 700 therapy have not been fully captured within the current cost and QALY estimates.

6 Innovation and lack of licensed treatment alternatives

DEX 700 is an innovative implant form of dexamethasone and adalimumab is currently the only licenced alternative for the treatment of posterior segment uveitis. Therefore, given the innovative nature of the technology and the acknowledgement that estimating the long-term benefits of treatment are uncertain, but that there is a significant risk of blindness for poorly controlled patients with posterior segment uveitis, Allergan considers that DEX 700 should be recommended by NICE for this indication.

The AG report notes that it is challenging to model the cost effectiveness of DEX 700 for bilateral disease given that the available data from HURON are based on treatment of one eye only. However, Allergan considers that it would be inappropriate to restrict access to treatment of only one eye for patients with bilateral disease because of uncertainty over the magnitude of the ICER. If neither dexamethasone nor adalimumab are recommended for patients with bilateral disease, this would lead to patients with the highest risk of incurring disability due to vision loss being left with no recommended licensed treatment option.

7 Exclusion of significant non-NHS costs and benefits

The AG report acknowledges that "*there are likely to be additional non-NHS and PSS costs and benefits of the interventions not captured within our analyses*." Substantial non-NHS costs and benefits are expected due to the working age population affected by posterior segment uveitis and the detrimental impact of the condition on work productivity. Further societal costs would be associated with blindness, including disability/ personal independence payments, housing benefits, council tax benefits and blind person's income tax allowances. Allergan therefore agrees that there are substantial non-NHS costs and benefits that are excluded from the current model (8). A study by Thorne et al. (2016) in the US has examined in detail the work productivity costs for patients with persistent posterior segment uveitis (9). The exclusion of substantial non-NHS and PSS costs and benefits provide a further rationale for why DEX 700 should be recommended by NICE as a treatment option for this indication.

8 Factual accuracy

Table 19 of the AG report states that 6/75 patients (8.0%) in the Sham arm of the HURON trial experienced serious AEs. This data corresponds to data included in the Allergan submission. However, after cross-checking this data against the CSR, this should be amended in both the submission and AG report to 5/75 patients (6.7%) with one patient experiencing multiple serious AEs.

9 References

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Adalimumab and dexamethasone for treating non-infectious uveitis [ID763]

Assessment Report comments from Birdshot Uveitis Society

General comments:

The report takes into account

- the lack of randomised clinical trial evidence
- the variety of designs and measurements in the selected randomised clinical trials
- the heterogeneous patient populations
- the small numbers of patients with different forms of non-infectious uveitis

and makes good use of input from expert clinical advisors.

However, the report does not recognise that

- patient benefit from both medications may be substantial in the rare diseases that together are termed 'non-infectious uveitis' although the uncertainty generated by a scant evidence base, especially regarding cost-effectiveness, makes patient benefit difficult to quantify meaningfully in this type of analysis
- the model of analysis based on 'permanent blindness versus remission versus death' does not reflect the reality of the day-to-day effects of the different degrees and progressions of visual impairment experienced by patients who are living with non-infectious posterior uveitis.

Specific comments:

1. Comparison of adalimumab with dexamethasone: this is referred to in several places, including p6 (2.2); p6 (2.3) and p167 (9). Comparison is inappropriate because of their different effects. The corticosteroid dexamethasone preparation is placed in the eye to quieten the inflammation of uveitis. The biologic adalimumab is injected subcutaneously to modify the body's underlying immune dysfunction which produces the inflammation of uveitis.
2. Place of adalimumab and dexamethasone in treatment pathways: on p23 (3.3) and p96 (5.2.3.2). Because of their different actions, selection of each product would be for different reasons and to produce different effects. They are unlikely to be used at the same point in any treatment pathway.
3. Stopping adalimumab treatment: p149 (6.2.2.1) notes that after two years of successful treatment, a proportion of patients would discontinue adalimumab because they had attained remission. However, the report makes no mention of stopping adalimumab treatment if a patient shows no response to it. Both these matters were addressed in the 2015 NHS England Clinical Commissioning Policy for adalimumab (https://www.engage.england.nhs.uk/consultation/specialised-services-consultation/user_uploads/uveitis-adults-policy.pdf) and the 2016 All Wales Therapeutics and Toxicology Centre decision on adalimumab (https://openrepository.awttc.org/app/serve/resource/gbmr3178). Both documents include the requirements that successful adalimumab treatment would be withdrawn after two years, and also that patients showing no benefit after three months' treatment would have adalimumab withdrawn. Incorporating both of these requirements into the cost-effectiveness calculations would reduce treatment costs.
4. Numbers of patients per annum eligible for treatment: p18 (3.1); p166 (8.4) and final sentence of p167 (9.1). These are patients experiencing worsening vision despite conventional treatment with corticosteroids and immunosuppressants. The numbers are small.

5. Effects of non-infectious uveitis on patients: p162 (6.2.3): sight problems and sight damage caused by uveitis can, and does, affect every aspect of daily life. It is not confined to a reduction in workplace productivity and effects on leisure time.
6. Costs of sight impairment: p11 (2.5) states that 'there are likely to be additional non-NHS and personal social services costs and benefits of the interventions not captured within our analyses.' Costs incurred through not approving these effective uveitis treatments, leaving patients to suffer increasing sight impairment, or costs avoided by approving these effective treatments, allowing patients to remain in employment and retain their independence, should have formed part of the report's cost-effectiveness calculations.
7. Converting VFQ-25 data to EQ-5D utilities: p118 (6.2.1.3) states that a 'new mapping method' was used, adding to the many other uncertainties identified in the report. QALY estimations are based on EQ-5D measures, but VFQ-25 data records the effects of uveitis and its treatments on the true quality of patients' vision and how it affects important daily activities.

[redacted]
Birdshot Uveitis Society
[redacted]

23rd January 2017

Response from Olivia's Vision to:

Assessment Report – Adalimumab dexamethasone for treating non-infectious uveitis. (ID 763).

General comments and existing provision.

We note the lack of comparative studies in uveitis which give reliable estimates of the efficacy, safety and cost effectiveness of other agents against which the results of VISUAL 1, VISUAL 11 and the Dex 700 arm of the Huron study may be compared. We further agree with the AG that a comparison of the two technologies with each other is of limited value given the different clinical indications for the use of each and the general treatment pathway currently followed and presented in Figure 2. However, given the potential flexibility in the use of these therapies in the treatment pathway, Table 2, permitted by their liscencing, there is a need to draw up clinical guidelines which allow an agreed range of options in the event routine funding of both becomes possible.

We cannot emphasise enough that currently, from the patient perspective, there is no third line therapy routinely funded for uveitis and in addition, in 2015, NHS England closed the IFR route to adalimumab for adult uveitis patients without a second condition. For the patient, a lot rides on the assessment of these therapies and as a uveitis charity, Olivia's Vision wants to see an end to clinical decisions based on the availability of regional funding rather than the clinical need of the patient.

In contrast to systemic inflammatory diseases, where biologics have transformed care over the past twenty years, the treatment of uveitis has remained largely unchanged and currently, the small number of patients who fail, or are intolerant of, second line therapies face the visual morbidity which the AG sets out for us in the studies referenced on pages 14-16 of their report.

Assessment of clinical effectiveness.

For patients with severe disease, visual acuity is an important outcome of treatment and if this is improved from baseline through successful cataract surgery, successful vitrectomy, resolution of macular oedema and reduction or quiescence of disease activity, then mental health often improves alongside visual function.

The results of the Huron, Dex 700, VISUAL 1 AND VISUAL 11 studies are significant for patients, especially those patients for whom nothing else has worked or for whom alternatives to ADA are contraindicated through side effects. The 46% chance of achieving drug induced remission reported by VISUAL 1 and the 61% chance of maintaining remission reported by VISUAL 11 are attractive options as is the resolution of macular oedema and increased BCVA reported by the Dex 700 study. It should be noted that maintaining quiescence is important since surgery for the complications of uveitis, such as cataract and glaucoma, is not usually attempted unless the uveitis has been inactive for at least three months.

The main reported patient outcome measure of improved visual function in the ADA treated arms of the VISUAL studies and the treated arm of the Dex 700 study does not surprise us. Patients with severe, intractable disease in contact with us worry most about their sight and how a drop in vision impacts their ability to work, drive and take care of their families. Most of these patients tell us they are depressed.

Our conclusion.

Although the AG's report suggests the need for further research and raises numerous questions concerning the impact of these treatments on sub groups of patients, patients with the most severe, refractory disease currently have limited treatment options. Given that the numbers are small, 175 estimated by Abbvie for ADA and 589 estimated by Allergan for dexamethasone, we believe these patients **must** be helped. Once second line agents, with or without corticosteroid, have failed, these patients are at grave risk of permanent loss of vision and mental health problems.

RNIB Supporting people with sight loss

Assessment Report consultation: Uveitis (non-infectious) – adalimumab and dexamethasone [763]

RNIB Response

Costs of sight loss

- The Assessment Report notes in section 2.5 Discussion (P.11) that the analysis presented takes "an NHS and PSS perspective. However, non-infectious uveitis affects a working-age population and can reduce workplace productivity. In addition, the disease can affect leisure time. Therefore, there are likely to be additional non NHS and PSS costs and benefits of the interventions not captured within our analyses."

- The report also notes that Uveitis is the fifth leading cause of visual impairment in developed countries and accounts for 10% of cases of legal blindness. Patients may experience sudden and temporary or progressive and permanent visual impairment and that prevelance among working aged population is high.

In the UK context, evidence shows that living with sight loss at working age substantially increases the cost of living.

Recent research shows that the budget for a working age person living alone who is eligible for certification as severely sight impaired with little or no sight is 60% more than for someone without that impairment (1).

Total additional costs per week compared to a sighted person (2):

- Sight impaired working age adult (previous research): £48.77
- Severely sight impaired working age adult: £116.43

1. Additional costs of living for people who are sight impaired or severely sight impaired – Research Findings 51 – Thomas Pocklington Trust 2016.
2. 'The additional cost of disability: a new measure and its application to sensory impairment (Hirsch and Hill 2016)' published in Disability and Society ISSN: 0968-7599.

Loss of sight has a substantial impact on quality of life. This is reflected in the high cost to society. The total cost of sight loss to the UK economy is in the region of £28 billion a year (3).

Sight impairment and severe sight impairment at working age and pensionable age are two potential consequences of uveitis therefore these costs must be taken into account in the cost benefit analysis.

3. State of the Nation Eye Health (2016) RNIB/Specsavers Transforming Eye Health.

Table 1a: Assessment Group response to Abbvie comments

Comment	Response
Issue 1. Vision loss rates may not be accurate	The AG recognise in the report that a key area of uncertainty is around the rate of blindness and the impact of the interventions upon that rate. This is the reason extensive exploratory analyses were undertaken around this. Compared with the study by Durrani et al. the study by Dick et al. includes a greater sample size (1,769), with patients who are followed up for longer and who all have posterior, intermediate or pan uveitis and are all adult patients with a mean age of 47. However, it is based upon insurance claims data within the US and the company state that based upon personal communication with the authors, [redacted] of patients receive biologics. The study by Durrani et al. is based in the UK at a tertiary referral uveitis service. The sample size is 315 patients who are followed up for a mean of 36.7 months, and 61% of the patients have posterior, intermediate or pan uveitis. In this study, not all patients are adults (mean age 48 years, age range 7 – 86) and treatment type is not reported. The clinical advisors to the AG believe that the estimate from either study could be possible. Importantly, it should be noted that there is no clinical trial evidence to show that either adalimumab or dexamethasone have any impact upon this rate of blindness. The AG do not find the argument to use the study by Durrani et al. sufficiently convincing to amend the base case; however the AG have now undertaken some additional analyses combining varying the relative risk of blindness in the adalimumab group at the same time as varying the remission rate. This has been done using both the study by Dick et al. and the study by Durrani et al. to represent the rate of blindness for the comparator. This analysis has been included in An aDDENDUM of the AG report.
Issue 2. Discontinue treatment with adalimumab in patients in quiescence (drug induced disease remission) is not included in the base case model	There is no evidence to suggest, if adalimumab were to be discontinued after two years, what the efficacy would be over time. It would be optimistic to assume in the base case that if patients enter remission for two years, the benefits of adalimumab will be sustained with no costs of further treatment being incurred. There are also mixed views between clinicians about whether adalimumab would be discontinued. The AG therefore believes that the current assumptions are appropriate within the base case. However, clearly this is highly uncertain, and the exploratory analysis shows the substantial impact upon the ICER of alternative assumptions.
Issue 3. Mapping VFQ-25 to EQ-5D	Since we do not compare dexamethasone and adalimumab directly, it is unimportant that different approaches were used to model the patient quality of life. The AG recognise on page 20 of the AG report that 'The EQ-5D utility also allows treatments to be compared with treatments for other diseases and patient populations, although it may not be as sensitive as the VFQ-25.'

	The AG requested patient level data from Abbvie prior to developing the model, in order to be able to analyse the relationship between VFQ-25 and EQ-5D; however this was not provided. We therefore undertook the analysis directly using the EQ-5D data, as well as undertaking a sensitivity analysis using the mapping of VFQ-25 to EQ-5D from HURON. The former was thought to be most appropriate for the base case analysis given that it was directly collected within the trial. The sensitivity analysis shows that the choice of approach is not a key driver of the model results (p139 – 140; 145).
Issue 5. Patients with pan-uveitis are not included as an important subgroup	Whilst there is evidence for the impact of adalimumab upon treatment failure for this subgroup, the relative treatment effect is smaller for pan uveitis patients. The reason provided by the company for undertaking this analysis is that pan uveitis patients have more serious disease and are more likely to suffer from severe vision loss. We do not have sufficient data to quantify either differences in quality of life of pan uveitis patients compared with posterior or intermediate uveitis patients, or differences in rates of permanent blindness. We therefore would not be able to capture the differences between pan uveitis and posterior and intermediate uveitis given current evidence.
Issue 6. The impact of vision loss (rather than blindness) on utility and costs is not included	Patient quality of life is directly taken from the VISUAL trials. Therefore any impact of vision loss on quality of life should be captured within the model. Costs associated with vision loss, borne by the NHS and PSS, are expected to be minimal.
Issue 7. Age at start of the model	The mean age in HURON was 44.8 (used within the base case) compared with 42.7 and 42.5 in the VISUAL I and VISUAL II trials respectively. The ICER for adalimumab compared with LCP(VI) in active uveitis patients was reduced from £95,506 to £94,126 per QALY when using a mean age of 42.7. The ICER for adalimumab compared with LCP(VII) in inactive uveitis patients was reduced from £321,405 to £314,131 per QALY when reducing the mean age from 44.8 to 42.5. The text has been made consistent within the report to be clear that the mean age in the base case is based on the mean age of patients in the HURON trial.
Issue 8. Impact of disease flares on vision loss is not included in the model	The impact of disease flares on vision loss is captured within the trial period using the health-related quality of life, and long term impacts are captured by altering the rate of blindness. Given current evidence, it is not possible to reasonably estimate any other long term impacts of the interventions.
Issue 9. Exclusion of costs of optical correction by spectacles post-cataract surgery for steroid-related cataract formation	The clinical advisors to the AG agree that after cataract operation almost everybody needs glasses for reading ('near correction'). However, in the older age group, everybody already has presbyopia (i.e. a reduced focal range which for most people means that reading glasses are needed). Thus, for the older population the need for reading glasses (or bifocals/varifocals) is not usually an additional expense. In the younger population (i.e. if having an operation below the age of around 40 years) which would apply to a proportion of uveitis patients (39% of patients in

	the study by Dick et al. are 44 years or less), there would usually be a small additional expense; however the total additional cost would have a minimal impact upon the cost of cataract surgery. In addition, it is understood that the individual rather than the NHS would fund the spectacles.
Issue 10. Exclusion of indirect cost of blindness in the model	The NICE methods guide states that a NHS and PSS perspective should be used as the reference case for decision problems where the intervention evaluated is solely commissioned by the NHS and does not have a clear focus on social care or public health outcomes. It states that 'The reference case is consistent with the NHS objective of maximising health gain from limited resources.' The AG is unfamiliar with the study by Green et al. and would need to undertake further literature searches in order to identify the most appropriate source of evidence and assess whether it is possible to reasonably quantify the impact of legal blindness upon productivity. Since a broader perspective is outside of the scope of the NICE process, the AG has not undertaken this substantial additional work.
Issue 11. Limited literature review	A thorough systematic review was conducted, with searches of nine databases plus additional search methods (e.g. checking an international database of clinical trials, citation checking, contacting clinicians). The last search update was run in October 2016. The search strategy was designed to retrieve studies of patients with uveitis and was not restricted to specific interventions or comparators. Inclusion criteria were designed to identify RCTs of adalimumab, dexamethasone, and any/all comparators relevant to the NICE scope. A total of 10,582 were retrieved and 134 full text articles were examined in detail. The VISUAL III extension study is included in the assessment report (section 5.2.2.6). Preliminary data on this study could not be used in the model because no data were reported according to initial allocation to adalimumab or placebo in VISUAL I and II, or according to which patients were initially active (in VISUAL I) or inactive (in VISUAL II).

Table 1b: AG response to Abbvie's minor clarifications and corrections

Section of the report	Description of the issue	Suggested change and justification of the amendment	AG response
The use of the terminology 'limited current practice'	The control arms from each trial (HURON, VISUAL I and VISUAL II) are described in the assessment report as limited current practice. This term is accompanied by denotation of which trial the limited current practice is referring to. However, using the same terminology is considered to be misleading to the reader as, in fact, the control arms in the HURON trial vs. the VISUAL trials are substantially different	AbbVie propose amending the term limited current practice to placebo, in order to avoid confusion	The AG used the term 'limited current practice' followed by the relevant trial name to be more explicit about what the comparator and intervention consisted of. The intention is to be clear that the comparator is not solely placebo and that the intervention also includes some immunosuppressant and corticosteroid use, which the use of 'placebo' for the comparator would not do. The AG believes that the use of the trial name following 'limited current practice' clearly suggests that the comparators are not the same. Moreover, adalimumab and dexamethasone are not directly compared within the analysis.
Page 6 and page 110-111	The AG report states that the de novo Markov model includes five health states: (i) treatment: no permanent blindness; (ii) treatment failure: no permanent blindness; (iii) permanent blindness; (iv) remission; and (v) death. In the Markov trace, however, the health states are (1) inconsistent with that stated in the report and (2) inconsistent between arms. Specific examples include the following: • In the dexamethasone vs sham trace there are three health states: Reduced sight, blindness, and death.	Health states should be consistently implemented and labelled across model arms. Alternatively, the AG report description of the health states should be updated to accurately reflect what is modelled.	The model is accurately described within the report. The model implementation (i.e. the Excel model) visually differs between adalimumab and dexamethasone because (a) dexamethasone patients are all assumed to 'fail' at the same time so there was no need to physically separate treatment and treatment failure out within the Markov trace of the model, and (2) because patients who have received a dexamethasone implant cannot enter the remission health state, and hence it is not included (rather than being a column of zeros). Both the assumptions for treatment failure and remission for each of

	• In the dexamethasone vs systemic steroids & Immunosuppressants trace there are three health states: On treatment, blind, and death • In the adalimumab vs systemic steroids & immunosuppressants trace the adalimumab arm follows the 5 state structure whereas the systemic steroids & immunosuppressants follow the 3 state structure		dexamethasone and adalimumab are clearly described within the report.
Impact of health problem (page 17) and significance for the NHS (page 18)	The burden of disease is not fully quantified. Impact of the health problem mentions that AEs associated with immunosuppressants can lead to substantial reductions in HRQOL. However, data is available which shows that patients with intermediate, posterior and pan-uveitis have poorer HRQOL compared with the general population and that visual impairment is a key factor in influencing HRQOL[1-4]. A post hoc analysis of HRQOL and patient reported outcomes (PRO) in patients with non-infectious intermediate or posterior uveitis participating in the HURON trial reports that QOL was significantly impaired in patients with uveitis when compared with the US general population ($p<0.001$)[3]. Significance for the NHS does not mention the financial impact of the complications of	Inclusion of studies detailed in Section 2.1.3 Impact of disease in the AbbVie submission.	The AG acknowledges that it was not explicitly specified that patients with uveitis have poorer HRQoL than the general population. We have therefore added the following text within the 'Impact of the health problem' section: "A post hoc analysis of HRQoL in patients with non-infectious intermediate or posterior uveitis participating in the HURON trial compared with a matched set of the general US population, reports that the uveitis group had lower mean scores on the following subscales of the VFQ-25: role-emotional ($P < .001$), mental health ($P < .001$), role-physical ($P < .001$), vitality ($P < .001$), general health ($P = .01$), and Mental Component Summary ($P < .001$). No statistically significant differences were found for the Physical Component Summary, physical functioning, bodily pain, and social functioning subscales of the VFQ-25, or EQ-5D scores.[3]"

	uveitis. Studies have demonstrated that healthcare and indirect (work loss/leaving the workforce) resource use and costs are significantly increased in patients with non-infectious intermediate, posterior and pan-uveitis compared with the general population[5] [6]. Patients with vision loss resulting from their disease have even higher healthcare costs[7].		The financial impacts of the complications of uveitis are considered in detail in Section 6 of the AG report. However, the AG acknowledges that these issues could also be highlighted within the 'significance for the NHS' section of the report. We have therefore added: "Patients require regular monitoring. There are substantial costs to the NHS and PSS associated with treatment of the complications of uveitis and blindness, as well as treatment for the adverse events associated with current practice."
Section 3.3, page 23	Adalimumab is administered as a subcutaneous injection containing 40 mg preparation of the active drug.	Would be clearer to explain the dosage regimen here The recommended dose of adalimumab for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting 1 week after the initial dose.	We agree with this comment. The text has been revised as follows: "Adalimumab is administered as a subcutaneous injection containing 40 mg preparation of the active drug. The recommended dose for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose."
Table 4, page 36	Information is missing on the number of patients from the UK in VISUAL I	[redacted] patients were enrolled in the UK (see Table 14.1_1.1 page 528 of the CSR)[8]	We agree with this comment. The text has been revised as follows in Section 5.2.2 (Assessment of effectiveness), under sub-section 5.2.2.1 Study characteristics: Two studies, VISUAL I[9] and VISUAL II[10] compared ADA administered subcutaneously as a 80 mg loading dose, then 40mg repeated every other week, with a corresponding placebo treatment in patients

			with active (VISUAL I)[9] or inactive (VISUAL II)[10] non-infectious intermediate, posterior or panuveitis. The treatment and follow-up period was up to 80 weeks (18 months) or until treatment failure. Main study data were available for 223 patients with active uveitis (study sites=67; UK, n= [redacted] patients;) [9 11] and 229 patients with inactive uveitis (study sites=62; UK, n=[redacted] patients). [10 12] VISUAL I[9] and VISUAL II[10] also included a sub-population of patients from Japan (n=16 patients and 32 patients, respectively).[11 12] However, data for this sub-group were not included in related publications[9 10] or the company submission.[13] One study, HURON[14] (study sites=46; n=229 patients), a 26-week Phase 3 trial, evaluated the effectiveness of two different dosages of DEX intravitreal implants, 0.7mg (DEX 700) and 0.35mg (DEX 350) compared to a sham procedure in patients with active, chronic non-infectious intermediate and posterior uveitis. Only data relating to the licensed DEX 700 arm are included in this review.
Table 4, page 36	Information is incorrect on the number of sites in VISUAL II	62 sites (see page 2 of published paper[10])	The AR did not present the number of study sites in VISUAL II. For clarity, the text in the report has been revised as above.
Page 45, paragraph 2	It is stated "priori sample size calculations for detecting between group differences for the specified primary outcomes at a significance level of 5% indicated that 234 patients were	This statement should read "138 patients were needed to achieve a power of 90% in VISUAL I"	Based on the information on page 355 (VISUAL I CSR), it was estimated that [redacted] treatment failure events were required to achieve a power of 90%,

	needed to achieve a power of 90% in VISUAL I;" Information is incorrect on the number of patients needed to achieve a power of 90%. There seems to be a misinterpretation of the sample size calculation in the protocol and the number of events. The CSR of VISUAL I[8], page 355, states that "For conservative purposes, it is assumed that failures will begin to occur after 2 months of study duration as the prednisone taper reaches lower doses. In addition, a pooled dropout rate of 35% over 12 months has been assumed. Using these failure rate assumptions for a log-rank test and a two-sided significance level of 5%, a total of 138 events are needed. The assumptions also include the following: • a power of 90%, • an average accrual rate of 4 subjects per month in the first 30 months and 7 subjects per month thereafter"		which translates to a sample size of approximately 234 subjects. For clarity, text has been revised to specify primary outcomes for VISUAL I, VISUAL II and HURON, as follows: "All studies reported pre-specified inclusion and exclusion criteria. *A priori* sample size calculations for detecting between group differences for the specified primary outcomes at a significance level of 5% indicated that 234 patients were needed to achieve a power of 90% in VISUAL I (outcome, time to treatment failure at or after 6 weeks);[9] 220 patients for 80% power in VISUAL II (outcome, time to treatment failure on or after 2 weeks)[10] and 73 patients per study arm to achieve power of 93% HURON (outcome, proportion of patients with a vitreous haze score of 0).[14]"
Table 7, page 46	Table 7 indicates that VISUAL I trial is not adequately controlled introducing a high risk of bias. AbbVie wish to highlight that based on the information in the point above (i.e. number of patients needed to achieve a power of 90%) VISUAL I is of adequate control	"Y" for VISUAL I, 4th quality assessment item	Table 7 has been amended on the basis that the study achieved the number of events required.

Page 67	Macular oedema VISUAL studies (page 67); do not mention pre-specified post hoc analyses of macular oedema in patients without macular hole and/or retinal detachment in VISUAL I. These analyses demonstrated that adalimumab did confer significant benefit over placebo in patients without macular hole and/or retinal detachment in VISUAL I.	Include data on pre-specified post hoc analyses of macular oedema in patients without macular hole and/or retinal detachment in VISUAL I, which can be found in Table 13 of the AbbVie submission.	The following text has been included in '*Macular oedema: VISUAL studies*': Additional post-hoc analyses presented by the company for patients without macular hole and/or retinal detachment in VISUAL I showed that ADA resulted in statistically significant reductions in time to OCT evidence of macular oedema in at least one eye on or after week 6 (HR, 0.33; 95%CI, 0.12 to 0.90); p=0.023) and the percentage change in CRT in each eye from best state achieved prior to week 6 to the final/ early termination visit (mean difference, -12.0; 95% CI, -21.5 to -2.5, p=0.014).[13]
Clinical section	VISUAL I and VISUAL II provide evidence for adalimumab in non-infectious intermediate, posterior and pan-uveitis. However, additional evidence is available from a retrospective audit of 41 patients in the UK on biologics.	Include data on the retrospective audit of 41 patients in the UK on biologics, which can be found on page 46 of the AbbVie submission (copy below). The Clinical Commissioning Policy for anti-TNF treatment options for adult patients with severe refractory uveitis contains details of a retrospective audit of data from a multicentre ocular inflammation biologics registry which captured routine clinical data in uveitis within the UK. Patients >18 years who received either	We have included non-RCT data presented in the relevant submission. Revisions in sections 5.2.2.4 (Effectiveness data from non-randomised studies of dexamethasone) as follows: New subheadings added: "5.2.2.4.1 DEX studies", inserted before text of summary of DEX non-RCT data "5.2.2.4.2 ADA studies" Followed by new text: Non-RCT data were presented in the company submission[13] and this was based on a retrospective audit presented in the Clinical Commissioning Policy for anti-TNF treatment options for adult patients with severe refractory uveitis[15]. The study evaluated data for patients > 18 years with different clinical forms of uveitis receiving ADA (40 mg/2 week) or infliximab (40 mg/2 week).

		adalimumab (40 mg every other week) or infliximab (3-5 mg/kg every 2 weeks) were included in the audit. All patients (n=41) on biologics showed clinical remission after a mean (± SD) follow-up of 1.36 (± 0.88) person years. More patients had an improvement in visual acuity than had worsening of visual acuity (48.8% versus 17.1%). Steroid dose was reduced to <10 mg prednisone in the majority of patients (88.9%) and almost half of patients (45.2%) stopped steroid use altogether. There was also a reduction in the use of immunosuppressants; 83.33% of patients on biologics had a reduction in the number and/or use of immunosuppressants.	The main findings of the audit were as follows: • Clinical remission of uveitis was observed in all patients (n=41) on biologics; (mean (±SD) follow-up period =1.36 (±0.88) person years). • 48.78% of patients experienced VA improvement; (mean ± SD follow-up of 2.51± 2.01 person years). • Fewer patients (17.07%) had worsening of VA; (mean ± SD follow-up period =4.38 ± 3.50 person years, • Patients receiving biologics, in due course, required less or reduced concomitant treatments. - 88.89% of patients showed reduction in steroid dose to ≤10 mg; (mean ± SD follow-up of 3.06 ± 2.32 person years) - 75.85% of patients showed reduction in steroid dose to ≤5 mg (mean ± SD follow-up of 3.15 ± 1.76 person years) - 45.16% of patients discontinued steroid treatment; (mean ± SD follow-up of 3.49 ± 1.59 person years) - 83.33% of patients showed reduction in the number and/or use of IMT: (mean ± SD follow-up of 1.54 ± 0.99 person years) • Patient-reported outcomes reported in the audit[15] are summarised as follows:

			- A significant decrease in vision-related quality of life (VCM) was directly associated with decrease in visual acuity in the worse eye within 1 year of starting biologics (p=0.0064). - Median vision-related VCM scores decreased with increasing follow-up time from time of starting treatment with biologics. - Mean SF-36 PCS scores (<47) were lower than those of the general population. However, the SF-36 MCS scores (>47) were higher than estimates for the general population, with an exception of scores obtained at year 3(duration of audit period, not reported).
Table 27, page 99	The clinical justification for not undertaking an indirect comparison is sensible; however, AbbVie would like to clarify why the AG initially considered an indirect comparison for the VFQ-25 outcome. In table 27 of the assessment report there are no values reported for the VFQ-25 composite score (change) for the DEX 700 arms of the HURON trial, making it difficult to understand why this outcome was initially considered for a potential indirect comparison. Furthermore, AbbVie would like clarification on how p	AbbVie propose that more clarification around the VFQ-25 composite score (change) from the HURON trial be included in the report. If this issue is caused by an error in reported values then AbbVie suggest correction to the assessment report be made.	The AG did not limit the outcomes to be considered for a mixed treatment comparison *a priori*. An indirect comparison was considered for VFQ-25 as this was an important outcome for estimating cost-effectiveness. Allergan provided the AG with patient-level data from the HURON trial at a sufficiently early stage in the process such that change in VFQ-25 could have been estimated by the AG and used in the indirect comparison. The p-values for the between-group differences in change in VFQ-25 composite score are reported in

	values for the non-reported VFQ-25 composite score (change) were estimated.		the HURON paper by Lightman et al.,[16] while the differences themselves are not reported.
Table 32, page 118 probability of AEs per cycle	The probability of fracture and diabetes for adalimumab, LCP(VI), and LCP(VII) in Table 32 are inconsistent with the probabilities used in the model (Excel tab: "CT, AEs & RT").	AbbVie wish this discrepancy to be addressed and the correct numbers to be reported	The AG acknowledges that the probabilities related to adalimumab and its comparators were not correctly reported in Table 32. The AG has amended Table 32 with the correct probabilities. The paragraph prior to the table has also been deleted as it incorrectly relates to this small difference.
Page 124, regression equation	The assessment report outlines a regression equation reported by Ara and Brazier that was used to estimate the age related utility that is applied in the model. The formula includes coefficients A, B and C as listed below: A = -0.0001728, B = -0.000034, C = 0.9584588 However, these coefficient values do not match those in the AG model. The parameter values are instead applied as: MaleCoefficient= 0.0212126 AgeCoefficient= -0.0002587 Age2Coefficient= -0.0000332.	AbbVie would like clarification on why the two sets of coefficients differ.	The AG acknowledges that the formula by Ara and Brazier was incorrectly reported in the report. The AG has corrected the formula in the report.
Table 67, page 217 and Table 68, page 218	The total QALYs, total costs, incremental QALYs, incremental costs and ICER in Table 67 (breakdown of the deterministic base case results for active population) and Table 68 (breakdown of the deterministic base case results for inactive population) do not match with the corresponding values in Table 48 (deterministic base case results for active population) and Table 58 (deterministic base	This discrepancy to be addressed and the correct numbers to be reported	The AG acknowledges that the cost and QALY breakdowns were not updated after the last changes to the model. The AG has updated Tables 66, 67 and 68.

	case results for inactive population), respectively.		
Deterministic sensitivity analysis, "DSA" tab, cell B15	Raised IOP is listed as a parameter to be tested in one way sensitivity analysis (OWSA) (cell B15 in the DSA tab). When varying base case values in the OWSA, the expectation is to vary parameters (for high and low values) without confidence intervals by a consistent percentage. The raised IOP mean value has been divided by 2 to estimate the low value and multiplied by 2 to estimate the high value.	AbbVie would like clarification for the rationale of dividing by 2 and multiplying by 2 to obtain the high and low values in the DSA. AbbVie also propose using the conventional percentage variation.	The AG acknowledges the inconsistency and has replaced the lower and upper values tested using the same rationale as the other parameters (the 95% CI based on the chosen distribution). The AG has accordingly changed Table 46 of the report, where the results of the DSA were presented.
Probabilistic distributions used for cost inputs in the AG model, "other" tab, row 28-41	The expected distribution to be applied to cost inputs is gamma and log normal. Where costs are considered in probabilistic sensitivity analysis, the gamma distribution has been applied. This is consistently the case in the cost tab. However, costs considered in the other inputs tab list NHS reference costs (row 28-41) and instead apply a normal distribution.	AbbVie would like clarification for the use of the normal distribution around cost inputs on the other inputs tab as mentioned in the description of the problem.	The AG believes that when the sample size is big enough it is justified to use a normal distribution based on the central limit theorem. This is not the case with all cost estimates, for which the AG has used the gamma distribution.

Table 2: Assessment Group response to Allergan comments

Comment	Response
The assessment group (AG) model indicates that the risk of blindness in the comparator group is one of the key drivers of ICER estimates. Allergan considers that the risk of blindness for the posterior segment uveitis target population would be somewhere between the estimates provided from all patients in the Dick et al. (2016) population and the tertiary referral population in Durrani et al. (2004). Therefore, the ICER for DEX 700 vs standard care is likely to be lower than the £20,058 base case deterministic estimate.	The AG recognise in the report that a key area of uncertainty is around the rate of blindness and the impact of the interventions upon that rate. This is the reason extensive exploratory analyses were undertaken around this. Compared with the study by Durrani et al. the study by Dick et al. includes a greater sample size (1,769), with patients who are followed up for longer and who all have posterior, intermediate or pan uveitis and are all adult patients with a mean age of 47. However, it is based upon insurance claims data within the US and the company state that based upon personal communication with the authors, 15% of patients receive biologics. The study by Durrani et al. is based in the UK at a tertiary referral uveitis service. The sample size is 315 patients who are followed up for a mean of 36.7 months, and 61% of the patients have posterior, intermediate or pan uveitis. In this study, not all patients are adults (mean age 48 years, age range 7 – 86) and treatment type is not reported. The clinical advisors to the AG believe that the estimate from either study could be possible. Importantly, it should be noted that there is no clinical trial evidence to show that either adalimumab or dexamethasone have any impact upon this rate of blindness.
The AG model shows that the ICER estimates for DEX 700 are highly sensitive to the relative risk of blindness for DEX 700 vs standard care. In the base case DEX 700 was modelled as reducing the risk of blindness vs standard care with a relative risk (RR) of 0.5 applying for 30 weeks then reverting to 1 after this period. It is argued that a reduced risk of blindness would be expected for patients beyond 30 weeks after each DEX 700 implantation. The rationale for DEX 700 having a longer-term impact on blindness is based on the ability of DEX 700 to reduce irreversible damage by controlling macular oedema.	The AG report is explicit that there is substantial uncertainty around both the rate of blindness for the comparator and the impact of the interventions upon this rate, due to the lack of long term data. The AG agrees that there is a clinical rationale for DEX 700 potentially reducing irreversible damage and hence impacting upon the relative risk of blindness beyond the trial data. This is actually consistent with the approach the AG originally wanted to take if evidence could have been identified linking macular oedema and other complications to blindness (see page 109-111 of the AG report). The simplified approach which was taken aims to allow the dexamethasone implant to have an impact upon the rate of blindness for the time that it is effective. In practice, there is likely to be a

	lag on this benefit, according to the time between the initial complication and blindness.
The AG model assumes that the duration of treatment effect of a single DEX 700 implant is 30 weeks for all patients in the base case. Utility and risk of blindness returns to baseline instantly after 30 weeks. Observational evidence indicates that the duration of treatment effect varies by patient. Data from a retrospective study conducted by Tomkins-Netzer et al. (2014) indicated that the median time to relapse for patients receiving DEX 700 was six months for the first implant but this ranged from two to 42 months and the overall relapse rate was only 69%. Data from a retrospective study conducted by Zarranz-Ventura et al. (2014) observed a median time to repeat implantation for patients receiving DEX 700 of 10 months (95% CI: 6.3 to 13.6 months). These data indicate that some patients will be controlled on DEX 700 for a longer period than 30 weeks and these benefits are not captured in the base case using a fixed treatment effect duration of 30 weeks for all patients. Sensitivity analyses presented in the AG report indicate that increasing the duration of treatment effect for DEX 700 beyond 30 weeks reduces the ICER markedly below the £20,058 estimate for the base case.	Given the evidence available, it was not possible to develop a patient-level model which could incorporate variability between patients. We have therefore developed a cohort model which uses patient averages. Whilst the benefits for some patients will be underestimated, for others the benefits will be overestimated. Based upon the evidence available and through discussions with their clinical experts, the AG believe that an average duration of benefit of 30 weeks is appropriate within the base case.
The AG model does not include the impact of malignancies for patients receiving standard care despite this being a risk for patients receiving long-term immunosuppressants. Yates et al. (2015) found that among patients treated with systemic immunosuppressants vs corticosteroids only, an additional 1.67 malignancies would be observed per 100 person-years. The avoidance of systemic adverse events is one of the key reasons why DEX 700 may be preferred over long-term systemic immunosuppressant therapy and it is argued that the immunosuppressant-sparing benefits of DEX 700 therapy have not been fully captured within the current cost and QALY estimates.	The AG was mindful that an important reason for the interventions being considered was to reduce the adverse events associated with steroids and immunosuppressants. As such, we went through an important process of identifying all possible adverse events based upon literature and clinical input, and then systematically excluding those which did not have substantial impacts upon costs. The AG considered including malignancy within the model; however the malignancy rates in HURON were not reported. If immunosuppressants were to have a small impact upon the risk of malignancy (as suggested by Yates et al), it is unclear whether a dexamethasone implant would reduce this risk given (a) the relatively short term nature of the implant and (b) the uncertainty around the extent that immunosuppressant use would be reduced.

	There was therefore insufficient evidence to incorporate an impact of dexamethasone upon malignancies within the model.
The immunosuppressant-sparing benefits of DEX 700 therapy have not been fully captured within the current cost and QALY estimates.	On page 118 of the AG report, we state 'The model includes the costs of the additional immunosuppressants provided to the proportion of patients receiving this rescue therapy.' Where we state in the AG report that 'If dexamethasone or adalimumab led to a reduction in the use of immunosuppressants and/or corticosteroids without this impacting upon efficacy in these treatment groups, then they would be more cost-effective than currently predicted', this refers to any additional impacts which are not captured by the HURON or VISUAL trials. The AG believe that the most appropriate assumption in the base case is that dexamethasone will not have a greater impact upon immunosuppressant use than captured within the HURON trial, given that we have no relative effectiveness evidence for any additional impacts on immunosuppressant use.
DEX 700 is an innovative implant form of dexamethasone and adalimumab is currently the only alternative licensed treatment for posterior segment uveitis. Therefore, given the innovative nature of the technology and the acknowledgement that estimating the long-term benefits of treatment are uncertain, but that there is a significant risk of blindness for poorly controlled patients with posterior segment uveitis, Allergan considers that DEX 700 should be recommended by NICE for this indication.	No response required.
The AG report notes that it is challenging to model the cost effectiveness of DEX 700 for bilateral disease given that the available data from HURON was based on treatment of one eye only. However, Allergan considers it would be inappropriate to restrict access to treatment of only one eye for patients with bilateral disease because of uncertainty over the magnitude of the ICER. If neither dexamethasone nor adalimumab are recommended for patients with bilateral disease, this would lead to patients with the highest risk of incurring disability due to	No response required.

vision loss being left with no licensed treatment option.	
The AG report acknowledges that there are likely to be additional non-NHS and PSS costs and benefits which are not captured in the model. Given the working age population affected by posterior segment uveitis, the detrimental impact of the condition on work productivity and the societal costs associated with blindness, Allergan considers that substantial non-NHS costs and benefits will be excluded from the AG model. These non-NHS and PSS costs and benefits provide a further rationale for the recommendation by NICE of DEX 700 for this indication.	No response required.
Table 19 of the AG report states that 6/75 patients (8.0%) in the Sham arm of the HURON trial experienced serious AEs. This data corresponds to data included in the Allergan submission. However, after cross-checking this data against the CSR, this should be amended in both the submission and AG report to 5/75 patients (6.7%) with one patient experiencing multiple serious AEs.	These data have been checked and changes made in the text and in Table 19.

Table 3: Assessment Group response to RNIB comments

Comment	Response
In the UK context, evidence shows that living with sight loss at working age substantially increases the cost of living. Recent research shows that the budget for a working age person living alone who is eligible for certification as severely sight impaired with little or no sight is 60% more than for someone without that impairment (1). Total additional costs per week compared to a sighted person (2): • Sight impaired working age adult (previous research): £48.77 • Severely sight impaired working age adult: £116.43 • Loss of sight has a substantial impact on quality of life. This is reflected in the high cost to society. The total cost of sight loss to the UK economy is in the region of £28 billion a year (3). Sight impairment and severe sight impairment at working age and pensionable age are two potential consequences of uveitis therefore these costs must be taken into account in the cost benefit analysis.	The model aims to capture any impacts of loss of sight upon quality of life (see 'quality of life' section, pages 112 – 117 of AG report). Whilst the report does highlight within the discussion section and the Executive Summary that 'there are likely to be additional non NHS and PSS costs and benefits of the interventions not captured within our analyses', the NICE methods guide states that a NHS and PSS perspective should be used as the reference case for decision problems where the intervention evaluated is solely commissioned by the NHS and does not have a clear focus on social care or public health outcomes. It states that 'The reference case is consistent with the NHS objective of maximising health gain from limited resources.' If a secondary analysis was undertaken to consider the societal perspective, given current evidence, there would be substantial uncertainty around the impacts of the interventions upon paid and unpaid work. The WPAI outcome reported in VISUAL I suggests that patients treated with adalimumab would have 10.6 fewer missed days at work than those receiving limited current practice. This aspect of reduced productivity could therefore be reasonably quantified. However, there is no evidence to quantify the impact of adalimumab use upon presenteeism (being at work with reduced productivity), unpaid work or leisure time. There is also no evidence to quantify the impacts of the dexamethasone implant upon paid or unpaid work. In addition, further literature searches would be required to assess whether it is possible to reasonably quantify the impact of legal blindness upon productivity. Thus, if this analysis was undertaken, the results would be highly uncertain, it would require substantial additional work, and it would be outside of the scope of the NICE process.

Table 4: Assessment Group response to Olivia's Vision comments

Comment	Response
For patients with severe disease, visual acuity is an important outcome of treatment and if this is improved from baseline through successful cataract surgery, successful vitrectomy, resolution of macular oedema and reduction or quiescence of disease activity, then mental health often improves alongside visual function. The results of the Huron, Dex 700, VISUAL I AND VISUAL II studies are significant for patients, especially those patients for whom nothing else has worked or for whom alternatives to ADA are contraindicated through side effects. The 46% chance of achieving drug induced remission reported by VISUAL I and the 61% chance of maintaining remission reported by VISUAL II are attractive options as is the resolution of macular oedema and increased BCVA reported by the Dex 700 study. It should be noted that maintaining quiescence is important since surgery for the complications of uveitis, such as cataract and glaucoma, is not usually attempted unless the uveitis has been inactive for at least three months. The main reported patient outcome measure of improved visual function in the ADA treated arms of the VISUAL studies and the treated arm of the Dex 700 study does not surprise us. Patients with severe, intractable disease in contact with us worry most about their sight and how a drop in vision impacts their ability to work, drive and take care of their families. Most of these patients tell us they are depressed.	Patient quality of life, including aspects of mental health, should be captured within the health economic model.

Table 5: Assessment Group response to Birdshot Uveitis Society comments

Comment	Response
The report takes into account • the lack of randomised clinical trial evidence • the variety of designs and measurements in the selected randomised clinical trials • the heterogeneous patient populations • the small numbers of patients with different forms of non-infectious uveitis and makes good use of input from expert clinical advisors.	No response required.
The report does not recognise that: • patient benefit from both medications may be substantial in the rare diseases that together are termed 'non-infectious uveitis' although the uncertainty generated by a scant evidence base, especially regarding cost-effectiveness, makes patient benefit difficult to quantify meaningfully in this type of analysis • the model of analysis based on 'permanent blindness versus remission versus death' does not reflect the reality of the day-to-day effects of the different degrees and progressions of visual impairment experienced by patients who are living with non-infectious posterior uveitis.	The AG report is very clear that patient benefit is difficult to quantify. The difficulty in measuring outcomes is discussed within the Background section on pages 18-20 under the heading 'Measurement of disease'. Within the cost-effectiveness section there is a section headed 'outcomes' on pages 103-104, and subsequent sections headed 'permanent legal blindness' 'adverse events' and 'quality of life' on pages 109-117 which describe the issues with quantifying patient benefit, as well as how they were quantified within the model. Moreover, a substantial number of sensitivity analyses were undertaken to show the impact of alternative model assumptions around patient benefit upon the model results. In addition, it is recognised within the Discussion section of the AR under the heading 'model perspective' that there are likely to be additional non NHS and PSS costs and benefits of the interventions not captured within our analyses (see other responses regarding this issue). The quality of life estimates taken from the trials should capture the different degrees of visual impairment experienced by patients. It is expected that there would be minimal additional costs to the NHS and PSS than already captured in the model for patients with visual impairment that are not legally blind.
<u>Comparison of adalimumab with dexamethasone:</u> this is referred to in several places, including p6 (2.2); p6 (2.3) and p167 (9). Comparison is inappropriate because of their different	No response required.

effects. The corticosteroid dexamethasone preparation is placed in the eye to quieten the inflammation of uveitis. The biologic adalimumab is injected subcutaneously to modify the body's underlying immune dysfunction which produces the inflammation of uveitis.	
Place of adalimumab and dexamethasone in treatment pathways: on p23 (3.3) and p96 (5.2.3.2). Because of their different actions, selection of each product would be for different reasons and to produce different effects. They are unlikely to be used at the same point in any treatment pathway.	No response required.
Stopping adalimumab treatment: p149 (6.2.2.1) notes that after two years of successful treatment, a proportion of patients would discontinue adalimumab because they had attained remission. However, the report makes no mention of stopping adalimumab treatment if a patient shows no response to it. Both these matters were addressed in the 2015 NHS England Clinical Commissioning Policy for adalimumab (https://www.engage.england.nhs.uk/consultation/specialised-services-consultation/user_uploads/uveitis-adults-policy.pdf) and the 2016 All Wales Therapeutics and Toxicology Centre decision on adalimumab (https://openrepository.awttc.org/app/serve/resource/gbmr3178). Both documents include the requirements that successful adalimumab treatment would be withdrawn after two years, and also that patients showing no benefit after three months' treatment would have adalimumab withdrawn. Incorporating both of these requirements into the cost-effectiveness calculations would reduce treatment costs.	Within the model, discontinuation of adalimumab was modelled based upon 'treatment failure' within VISUAL I and II (see pages 106-109, 'treatment discontinuation'). This includes any patients which did not respond to treatment. Our clinical experts suggested that in practice the criteria for treatment discontinuation may not be as strict as in the VISUAL trials; however since the effectiveness of adalimumab was based upon these trials, for consistency it was necessary to use the same treatment discontinuation criteria. This issue is discussed in the Discussion of the Executive Summary (page 10), as well as Section 6.2.3 (page 148, 'Use of adalimumab and dexamethasone in clinical practice').
Numbers of patients per annum eligible for treatment: p18 (3.1); p166 (8.4) and final sentence of p167 (9.1). These are patients experiencing worsening vision	No response required.

despite conventional treatment with corticosteroids and immunosuppressants. The numbers are small.	
Effects of non-infectious uveitis on patients: p162 (6.2.3): sight problems and sight damage caused by uveitis can, and does, affect every aspect of daily life. It is not confined to a reduction in workplace productivity and effects on leisure time.	The quality of life impacts of uveitis should be reasonably captured in the quality of life measures within the trials. The point being made on p162 mainly relates to the perspective taken within the health economic modelling, and key additional costs which might be incurred by taking a societal perspective. This text has been modified to state that "Currently, the base case analysis takes an NHS and PSS perspective. However, sight problems and sight damage caused by uveitis can affect every aspect of daily life. The quality of life measures used within the health economic model aim to largely capture these effects. However, if a societal perspective was taken, the cost-effectiveness of the interventions would be reduced. A societal perspective would capture the additional cost savings associated with increased leisure time and workplace productivity resulting from the benefits of the interventions. Given that non-infectious uveitis affects a working-age population these cost savings would not be negligible. Therefore, there are likely to be additional non NHS and PSS costs and benefits of the interventions not captured within our analyses; however these additional costs are beyond the scope of a NICE appraisal."
Costs of sight impairment: p11 (2.5) states that 'there are likely to be additional non-NHS and personal social services costs and benefits of the interventions not captured within our analyses.' Costs incurred through not approving these effective uveitis treatments, leaving patients to suffer increasing sight impairment, or costs avoided by approving these effective treatments, allowing patients to remain in employment and retain their independence, should have formed part of the report's cost-effectiveness calculations.	The NICE methods guide states that a NHS and PSS perspective should be used as the reference case for decision problems where the intervention evaluated is solely commissioned by the NHS and does not have a clear focus on social care or public health outcomes. It states that 'The reference case is consistent with the NHS objective of maximising health gain from limited resources.' If a secondary analysis was undertaken to consider the societal perspective, given current evidence, there would be substantial uncertainty around the impacts of the interventions upon paid and unpaid work. The WPAI outcome reported in VISUAL I suggests that patients treated with adalimumab would have 10.6 fewer missed days at work than those receiving limited current practice. This aspect of reduced productivity could therefore be reasonably quantified. However, there is no evidence to quantify the impact of adalimumab use upon presenteeism (being at work with reduced productivity), unpaid work or leisure time. There is also no evidence to quantify the impacts of the dexamethasone implant upon paid or unpaid work. In addition, further literature

	searches would be required to assess whether it is possible to reasonably quantify the impact of legal blindness upon productivity. Thus, if this analysis was undertaken, the results would be highly uncertain, it would require substantial additional work, and it would be outside of the scope of the NICE process.
Converting VFQ-25 data to EQ-5D utilities: p118 (6.2.1.3) states that a 'new mapping method' was used, adding to the many other uncertainties identified in the report. QALY estimations are based on EQ-5D measures, but VFQ-25 data records the effects of uveitis and its treatments on the true quality of patients' vision and how it affects important daily activities.	The AG recognises that the VFQ-25 is more sensitive to vision-related quality of life than the EQ-5D. The VFQ-25 outcomes are reported in the clinical section in addition to the EQ-5D outcomes. However, in order to compare the cost-effectiveness of these treatments with other treatments for different patient populations and indications, a standard outcome measure is required. The NICE methods guide states that 'Given the need for consistency across appraisals, one measurement method, the EQ-5D, is preferred for the measurement of health-related quality of life in adults.' The NICE methods guide also states that 'In some circumstances the EQ-5D may not be the most appropriate. To make a case that the EQ-5D is inappropriate, qualitative empirical evidence on the lack of content validity for the EQ-5D should be provided, demonstrating that key dimensions of health are missing. This should be supported by evidence that shows that EQ-5D performs poorly on tests of construct validity and responsiveness in a particular patient population.' Several published studies show that there is a strong association between VFQ-25 and EQ-5D values. Moreover, the statistical analysis undertaken using the patient-level data from HURON used in the AG analysis suggests that there is a statistically significant relationship between the two outcome measures.

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ERRATUM

Title: Adalimumab and dexamethasone for treating non-infectious intermediate, posterior or pan uveitis in adults

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Hazel Squires, Senior Research Fellow, ScHARR Edith Poku, Research Fellow, ScHARR Inigo Bermejo, Research Associate, ScHARR Katy Cooper, Senior Research Fellow, ScHARR John Stevens, Reader in Decision Science, ScHARR Jean Hamilton, Research Associate, ScHARR Ruth Wong, Information Specialist, ScHARR Alastair Denniston, Consultant Ophthalmologist (Uveitis and Medical Retina), University Hospitals Birmingham NHS Foundation Trust, UK Ian Pearce, Director of Clinical Eye Research Centre, St Paul's Eye Unit, Royal Liverpool University Hospital, UK Fahd Quhill, University Senior Lecturer and Consultant Ophthalmologist (Specialist interest in Medical Retina), Sheffield Teaching Hospitals NHS Foundation Trust, UK
Correspondence Author	Hazel Squires, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, S1 4DA UK. Email: h.squires@sheffield.ac.uk
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over a 4-month period between August and November 2005; estimates ranged from 2 to 59 per 100,000 people.[27] A claims-based analysis conducted in the USA based on 2012 data from the OptumHealth Reporting and Insights claims database reported overall the prevalence of adult non-infectious uveitis (n=4,827 cases; 2,086 men and 2,741 women) to be 121 cases per 100,000 people (95% confidence interval (CI) 117.5 to 124.3).[28] Observed prevalence rates of non-infectious intermediate, posterior and pan-uveitis in adults were 1 (95% CI 0.8-1.5), 10 (95% CI 9.4-11.5), and 12 (95% CI 10.6-12.7) per 100,000 people, respectively.[28] Earlier studies generally provided no or limited data for patients with non-infectious uveitis[29, 30] or had issues (e.g. missing data, use of administrative data, variations in referral patterns) making estimates less generalisable.[27,28,31] Between 3 and 16 out of 100,000 people are estimated to have non-infectious posterior segment-involving uveitis (see Section 7).

Impact of health problem

Uveitis is the fifth leading cause of visual impairment in developed countries and accounts for 10% of cases of legal blindness.[28,32] Patients may experience sudden and temporary or progressive and permanent visual impairment.[16]

By anatomic classification of uveitis, patients with posterior segment-involving uveitis and panuveitis tend to suffer more severe visual impairment than those with anterior uveitis.[32] Compared with uveitis affecting only the posterior segment, patients with panuveitis (both posterior and anterior) tend to have a poorer prognosis.[16] Additionally, the underlying cause of uveitis may also significantly influence the prognosis of intraocular inflammation.[16] For example, patients with uveitis due to Behcet's disease have poorer visual outcomes even when intense treatment is initiated at early stages of the disease compared with patients with non-infectious uveitis without an associated systemic condition.[16] Complications of uveitis, namely cystoid macular oedema, cataract, glaucoma or a combination of any of these significantly influence the visual morbidity.

A post hoc analysis of HRQoL in patients with non-infectious intermediate or posterior uveitis participating in the HURON trial compared with a matched set of the general US population, reports that the uveitis group had lower mean scores on the following subscales of the VFQ-25: role-emotional ($P < .001$), mental health ($P < .001$), role-physical ($P < .001$), vitality ($P < .001$), general health ($P = .01$), and Mental Component Summary ($P < .001$). No statistically significant differences were found for the Physical Component Summary, physical functioning, bodily pain, and social functioning subscales of the VFQ-25, or EQ-5D scores.[33]

Loss of visual function can lead to the inability to work and the inability to drive. It can also affect the ability to take part in leisure activities. In addition, the currently available treatments, including corticosteroids and immunosuppressants, are associated with substantial adverse events (AEs). The most common AEs associated with long-term use of corticosteroids include osteoporosis and fractures, gastric conditions, psychiatric conditions, skin conditions, hyperglycaemia, weight gain, ocular conditions (including cataract) and cerebrovascular disease.[34] The most common AEs associated with immunosuppressants include cataract, ocular hypertension, headache, fever, nausea, diarrhoea, fatigue, paraesthesia, tremors and systemic infection.[35, 36] These can lead to substantial reductions in health-related quality of life for the patient and may also impact upon the patient's family.

Significance for the NHS

Patients with uveitis often require referral to secondary care to confirm diagnosis and provide treatment. Patients require regular monitoring. There are substantial costs to the NHS and PSS associated with treatment of the complications of uveitis and blindness, as well as treatment for the adverse events associated with current practice. As the cause and presentation of uveitis varies between individuals, it is important for clinicians to have a range of treatment options available. In practice, a range of unlicensed immunosuppressants and corticosteroids are used to treat patients with uveitis. Clinical advisors to the AG suggest that dexamethasone implants and adalimumab are both used variably in current practice depending on funding availability. The number of patients that would be eligible for these treatments annually is uncertain, but Allergan and Abbvie estimate that it would be 589 and 175 patients for dexamethasone and adalimumab respectively (see Section 7).

Measurement of disease

Outcome measures in uveitis may be grouped according to the different aspects that they measure: (1) disease activity or inflammation in the eye (e.g. VH, which is the degree of cloudiness in the vitreous humour; and acute cystoid macular oedema); (2) disease-associated tissue damage or complications (e.g. cataract; glaucoma; chronic cystoid macular oedema); (3) visual loss (e.g. visual acuity; visual field loss); and 4) patient-reported visual function (e.g. via the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25)).[37]

There are some issues worth highlighting about outcome measurements in patients with uveitis. Vision loss has a complex interaction with visual acuity (which is a measure of central vision according to a validated measure such as the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, Snellen chart or another similar tool), visual field contrast sensitivity and colour vision. Visual acuity in patients with uveitis may reflect both the degree of intraocular

inflammation and the extent of damage in the eye; whereas inflammation may vary over short time periods (days or weeks), damage may accrue slowly (months or years) and, with the important exception of cataract and acute cystoid macular oedema, is usually irreversible. It will be immediately evident that whereas short-term effects on vision (related to inflammation) may be captured within a clinical trial, the commonly used time-frames in studies are too short to capture important long-term consequences on vision of damage to the eye caused by inadequately controlled uveitis. This may lead to systematic underestimates of the effects of such interventions in clinical trials.

Markers of structural damage to the eye, such as macular oedema (swelling of the retina), cataract and glaucoma, are important outcomes because they are the mechanisms by which uveitis patients lose vision, and are objective measures. However, these may not be good markers of whether a treatment reduces inflammation because they indicate structural damage to the eye, which might not resolve when the inflammation is treated.

In clinical practice, a combination of several outcomes is used to assess response of uveitic activity to treatment. Generally, outcomes related to uveitis are assessed by clinical examination (visual acuity, slit-lamp examination of AC cells, VH grading) and by imaging (e.g. optical coherence tomography).

The NEI system for VH grading and AC cell grading proposed by the Standardisation of Uveitis Nomenclature (SUN) Working group[13] is the '*current gold standard'* for assessing intraocular inflammation (i.e. AC cell grade and VH grade)[38] The SUN system was a formalisation and adoption of the Nussenblatt scale.[39, 40] Grading requires the examination of the patient's eye by an indirect ophthalmoscope followed by a comparison of the appearance with a series of photographs of varying grades of fundus VH.[39] Although, the grading system is accepted by the Food and Drug Administration and has been used on a number of recent studies of uveitis,[38] it is a subjective grading of cloudiness in the vitreous humour caused by inflammatory cells and cell debris on a non-continuous scale (0, 0.5+, 1, 2, 3 and 4+).[12, 13, 37, 41] Its poor discriminatory property for detecting changes in the lower VH grades coupled with extensive inter-rater variations have been reported as some of its limitations.[38, 42, 43]

Inflammation in the AC is assessed on the basis of number of cells per 1 field on standard slit-lamp examination or by high-speed optical coherence tomography.[40]

Complications of structural changes in the eye due to uveitis are typically reported according to the type of complication. For example, the SUN Working Group suggests that macular

oedema could be determined by clinical examination and additional tests, for example optical coherence tomography or fluorescein angiography.[13] A patient is considered to have an increased or elevated intraocular pressure (IOP) if the pressure rises above a specified limit or increases from a baseline value in a study where patients are followed over time (i.e. longitudinal data).[13] While there is no consensus reached on the threshold for considering an increase in intraocular pressure, an increase of 10 mmHg or more is considered to be important.[13] However, SUN group recommends the reporting of IOPs above the following thresholds:[13] 21 mm Hg (above the accepted upper limit of normal); 24 mm Hg (associated with a significant risk of glaucoma); and 30 mm Hg (when treatment for raised IOP is often started).

Other outcomes reported in studies of patients with uveitis include generic utility measures such as EQ-5D and vision-specific measures such as the VFQ.[44] These outcome measures capture broader considerations and hence may overcome some of the issues associated with the alternative outcome measures. The EQ-5D utility also allows treatments to be compared with treatments for other diseases and patient populations, although it may not be as sensitive as the VFQ-25.[45]

3.2 Current service provision

Non-infectious intermediate, posterior and panuveitis are initially treated with corticosteroids. Corticosteroids may be administered systemically (oral or parenteral), or locally via periocular or intravitreal injections or intravitreal implants. Additionally, if the front of the eye is also affected, topical corticosteroids and dilating eye drops may be offered. Systemic corticosteroids carry significant morbidity (e.g. cataract, glaucoma, diabetes, osteoporosis, weight gain, raised blood pressure) and long-term use above 7.5mg per day is not recommended.[46, 47]

In terms of second-line treatment, people with severe or chronic non-infectious uveitis, whose disease has not adequately responded to corticosteroid treatment, for whom corticosteroids are not appropriate, or whose uveitis recurs after tapering the corticosteroid dose, may be given immunosuppressive drugs (such as methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus and azathioprine). Immunosuppressive drugs can allow a reduction in the corticosteroid dose and associated complications. If the disease does not respond to these treatments or if they are not tolerated, especially in patients at high risk of losing their vision or those with systemic disease related to uveitis, biological TNF-alpha inhibitors may be used. The majority of these treatments are not currently licensed.

National guidelines on treating non-infectious uveitis do not currently exist; however, all three clinical advisors to the AG, who practice within different regions in the UK (Birmingham,

Liverpool, Sheffield), were in agreement that the above description represents the general treatment pathway. The description is also consistent with three local treatment pathways, two referenced in the dexamethasone submission[48] (North East Retinal Group and NHS Southern Derbyshire Clinical Commissioning Group)[1, 2] and one obtained via personal communication from Alastair Denniston (August 2016) (West Midlands Regional Uveitis Service). The general treatment pathway does not differ dependent upon whether a patient has intermediate, posterior or panuveitis. However, specific treatment is individualised based upon a broad range of factors. In particular, treatment depends upon whether or not systemic disease is known to be present, whether any systemic disease is controlled (i.e. whether or not current inflammation is restricted to the eye), and whether the disease affects one or both eyes. **Error! Reference source not found.** shows the general treatment pathway developed based upon three local pathways and input from the clinical advisors to the AG.

The following terminology is used in this report:

- **Systemic disease:** Known underlying systemic disease related to the uveitis
- **Active systemic disease:** Systemic disease which is currently requiring treatment (in these patients, systemic treatment may be more appropriate to treat both the uveitis and the underlying disease)
- **No active systemic disease:** Either no systemic disease related to uveitis, or systemic disease which is currently controlled (in these patients, treatment local to the eye may be more appropriate)
- **Local treatment / local pathway:** Treatments which are local to the eye (may be given to one or both eyes; little effect on systemic disease)
- **Systemic treatment / systemic pathway:** Treatments which are given systemically (and by their nature treat both eyes and may also treat systemic disease)
- **Unilateral:** Uveitis affecting one eye. This does not relate to treatment for one eye
- **Bilateral:** Uveitis affecting both eyes. This does not relate to treatment for both eyes. In the case of local treatment, it may be for one or both eyes and will be referred to as such
- **Legal blindness:** BCVA of 20/200 or less in the better-seeing eye and/or a visual field of 20 degrees or less

3.3 Description of technology under assessment

Adalimumab (Humira, AbbVie) is a monoclonal antibody that inhibits the pro-inflammatory cytokine, TNF-alpha. Adalimumab has a marketing authorisation from the European Medicines Agency (EMA) for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing or in patients for whom corticosteroid treatment is inappropriate.[3] Adalimumab is administered as a subcutaneous injection containing 40 mg preparation of the active drug. The recommended dose for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose.

Dexamethasone intravitreal implant (Ozurdex, Allergan) is a corticosteroid which suppresses inflammation by inhibiting the expression of pro-inflammatory mediators. Dexamethasone implant has a marketing authorisation from the EMA for treating adults with inflammation of the posterior segment of the eye presenting as non-infectious uveitis (i.e. intermediate, posterior and panuveitis). Dexamethasone intravitreal implant is a biodegradable ophthalmic implant which contains 0.7mg of the active drug. Each implant is intravitreally administered using a single-use solid polymer drug delivery system or applicator.[6] The Summary of Product Characteristics (SmPC) for dexamethasone notes that administration to both eyes concurrently is not recommended due to lack of data.[6]

Place of the interventions in the treatment pathway

Clinical advisors to the AG and three local treatment pathways[1, 2] from the North East Retinal Group and the NHS Southern Derbyshire Clinical Commissioning Group[1, 2] (as referenced in the dexamethasone submission)[48] and the West Midlands Regional Uveitis Service (personal communication from clinical advisor) were consulted to determine the place of the interventions in the treatment pathway. A general view was that dexamethasone and adalimumab would generally not be used for the same patients or at the same point in the pathway. Treatments local to the eye (including the dexamethasone implant) are considered to be appropriate for unilateral uveitis or asymmetric bilateral uveitis (where disease is more severe in one eye), where systemic disease is not present or is well-controlled. Systemic treatments (including adalimumab) are considered to be appropriate to treat patients with bilateral uveitis (i.e. affecting both eyes) and/or active systemic disease. According to clinical advice to the AG, systemic treatments would generally not be given to a patient with unilateral uveitis and no active systemic disease, because of the adverse effects associated with them. Patients with bilateral uveitis but no active systemic disease could be treated via either a local or systemic approach. Whilst the inclusion criteria for the clinical trials of these drugs were not limited by these factors, our clinical experts suggest that clinicians may have selected patients for the trials accordingly.

In addition, the licensing of adalimumab and dexamethasone differ in that to be eligible for adalimumab, patients must have had an inadequate response to corticosteroids, require steroid-sparing treatment, or corticosteroid treatment must be inappropriate, whereas dexamethasone implants could be used first-line. Clinical advisors to the AG suggest that in practice it is likely that dexamethasone would be used second-line following local or systemic corticosteroids, whilst adalimumab would be used as a third-line option for patients with insufficient control with, or intolerance to, systemic corticosteroids and immunosuppressants; however, for some patients this may be as a result of current funding availability rather than clinical need. Figure 2 shows the general treatment pathway with the most likely place of dexamethasone and adalimumab (based on the opinion of the clinical advisors to the AG).

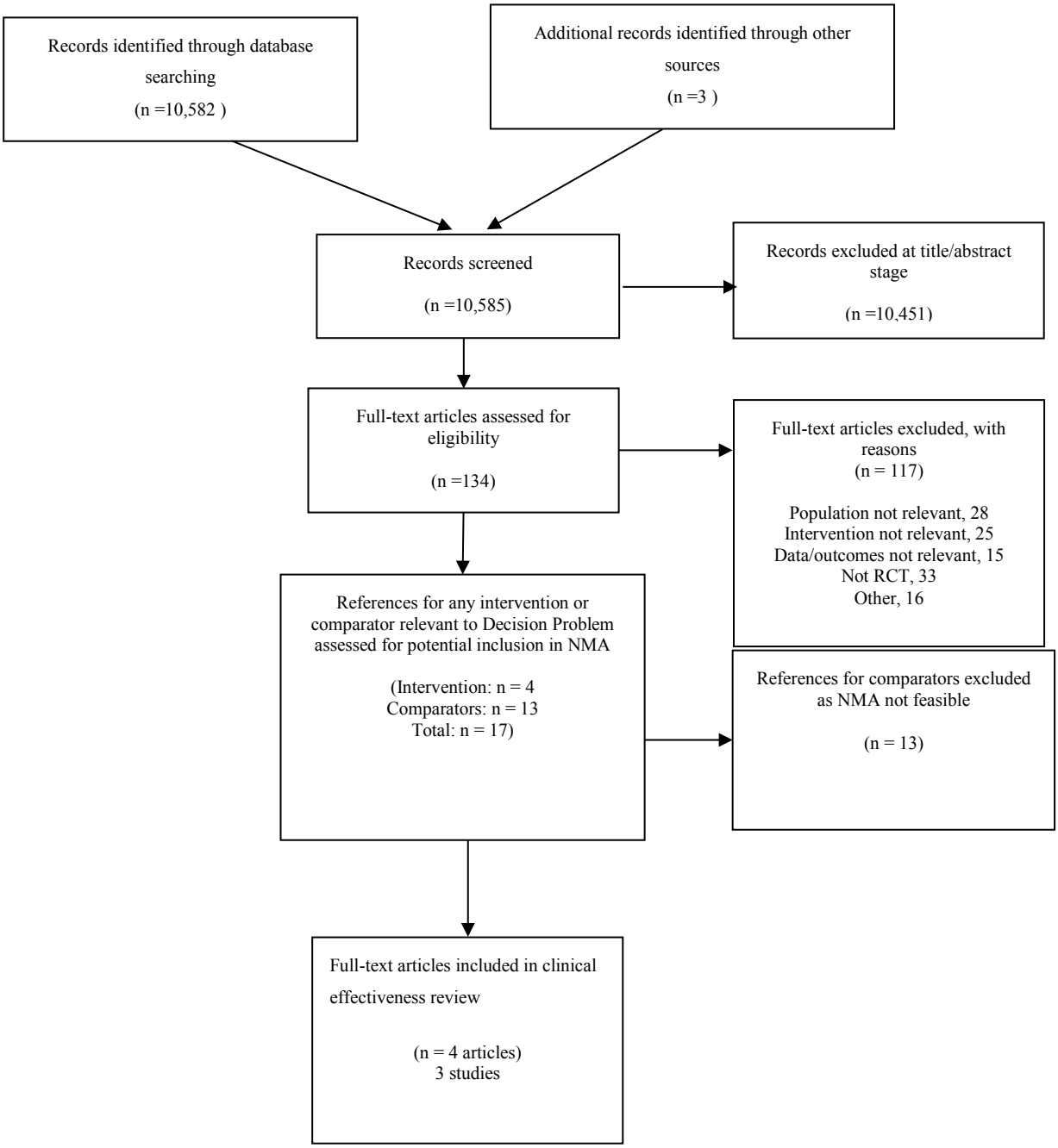
Whilst for most patients there is a clear clinical rationale for providing dexamethasone and adalimumab at different points in the treatment pathway and for different reasons, the licensing allows both treatments to be given at overlapping points in the pathway (i.e. for patients with inadequate response to corticosteroids, in need of corticosteroid-sparing or in whom corticosteroid treatment is inappropriate),[3] although dexamethasone implant is also licensed in a less restricted group.[6] This overlap is reflected somewhat by their use in clinical trials (see Section 5). **Error! Reference source not found.** presents the situations in which adalimumab and dexamethasone may be used according to both licensing and clinical appropriateness. The most likely places in the pathway where these treatments would be used according to clinicians are shown in bold.

Table 1: Situations in which adalimumab and dexamethasone may be used

	Unilateral (or temporary flare in one eye)* **No active systemic disease**	**Bilateral** **No active systemic disease**	**Unilateral (or temporary flare in one eye)** **Active systemic disease**	**Bilateral** **Active systemic disease**
Line of therapy (see Error! Reference source not found.**):**	Local treatment appropriate	Systemic or local treatment appropriate	Systemic treatment appropriate	Systemic treatment appropriate
First line	Dexamethasone or Adalimumab licensed if corticosteroid treatment is inappropriate			Adalimumab licensed if corticosteroid treatment is inappropriate
Second line (after systemic corticosteroids)	**Dexamethasone** or Adalimumab◊	**Dexamethasone** or Adalimumab◊	**Dexamethasone** or Adalimumab◊	Adalimumab
Third line (after systemic corticosteroids and immunosuppressants)	Dexamethasone or Adalimumab◊	Dexamethasone or **Adalimumab**	Dexamethasone or **Adalimumab**	**Adalimumab**

*Adalimumab is not clinically appropriate for unilateral non-systemic disease due to side effect profile of systemic therapies
∝Dexamethasone is not clinically appropriate for control of active systemic disease
◊In practice adalimumab would only be used if there was a specific contraindication to dexamethasone

Figure 1: PRISMA flow chart



5.2.2 Assessment of effectiveness

5.2.2.1 Study characteristics

The characteristics of the two included studies of ADA and one study of DEX 700 in patients with non-infectious uveitis are summarised in **Error! Reference source not found.**.

Two studies, VISUAL I[4] and VISUAL II[5] compared ADA administered subcutaneously as a 80 mg loading dose, then 40mg repeated every other week, with a corresponding placebo treatment in patients with active (VISUAL I)[4] or inactive (VISUAL II)[5] non-infectious intermediate, posterior or panuveitis.

The treatment and follow-up period was up to 80 weeks (18 months) or until treatment failure. Main study data were available for 223 patients with active uveitis (study sites=67; UK, n= [redacted] patients;) [4,51] and 229 patients with inactive uveitis (study sites=62; UK, n=[redacted] patients).[5,55] VISUAL I[4] and VISUAL II[5] also included a sub-population of patients from Japan (n=16 patients and 32 patients, respectively).[51, 55] Data for this sub-group were not included in related publications[4, 5] or the company submission.[56]

One study, HURON[7] (study sites=46; n=229 patients), a 26-week Phase 3 trial, evaluated the effectiveness of two different dosages of DEX intravitreal implants, 0.7mg (DEX 700) and 0.35mg (DEX 350) compared to a sham procedure in patients with active, chronic non-infectious intermediate and posterior uveitis. Only data relating to the licensed DEX 700 arm are included in this review.

arms was stratified according to prior immunosuppressant treatment in the VISUAL studies;[4, 5] conversely, randomisation was stratified according to baseline VH in the HURON study.[7] Blinding of participants and investigators was assessed as satisfactory across studies. In the VISUAL studies,[4, 5] unmasking of treatment allocation was only permitted in the event of a medical emergency. In the HURON study,[7] treatment investigators were responsible for the implantation procedure; however, outcome assessors were masked to treatment received by patients.

All studies reported pre-specified inclusion and exclusion criteria. *A priori* sample size calculations for detecting between group differences for the specified primary outcomes at a significance level of 5% indicated that 234 patients were needed to achieve a power of 90% in VISUAL I (outcome, time to treatment failure at or after 6 weeks);[4] 220 patients for 80% power in VISUAL II (outcome, time to treatment failure on or after 2 weeks)[5] and 73 patients per study arm to achieve power of 93% HURON (outcome, proportion of patients with a vitreous haze score of 0).[7] Based on this, VISUAL I[4] randomised 223 patients, slightly fewer than the 234 suggested by the power calculation. Demographic and baseline characteristics between study arms were comparable for all studies with the exception of duration of uveitis which was slightly longer in the non-active comparator arms as noted above. The impact of non-study treatments options available throughout the study duration is unclear, in particular in the HURON study,[7] in which patients with worsening of intraocular inflammation following implantation procedure could receive rescue (escape) medication comprising systemic corticosteroids or immunosuppressants or topical steroids. Indications for escape medication were early treatment failure (i.e. patients with VH increase ≥1 units from baseline, at week 3) or late treatment failure (i.e. patients with VH grade, at least 1.5+, at week 8 or after week 8).

The VISUAL I and II[4, 5] studies did not include data for patients in the Japanese sub-studies in their analyses. In HURON,[7] 100% of patients were included in intention-to-treat analyses, while the analyses described as "intention-to-treat" in the VISUAL studies[4, 5] excluded 6 of 223 patients (3%) in VISUAL I[4] and 3 of 229 patients (1%) in VISUAL II[5] because of "incomplete efficacy data and compliance issues at these sites".

Figure 2: Summary of methodological quality of included studies: review authors' judgement about each quality item across included studies

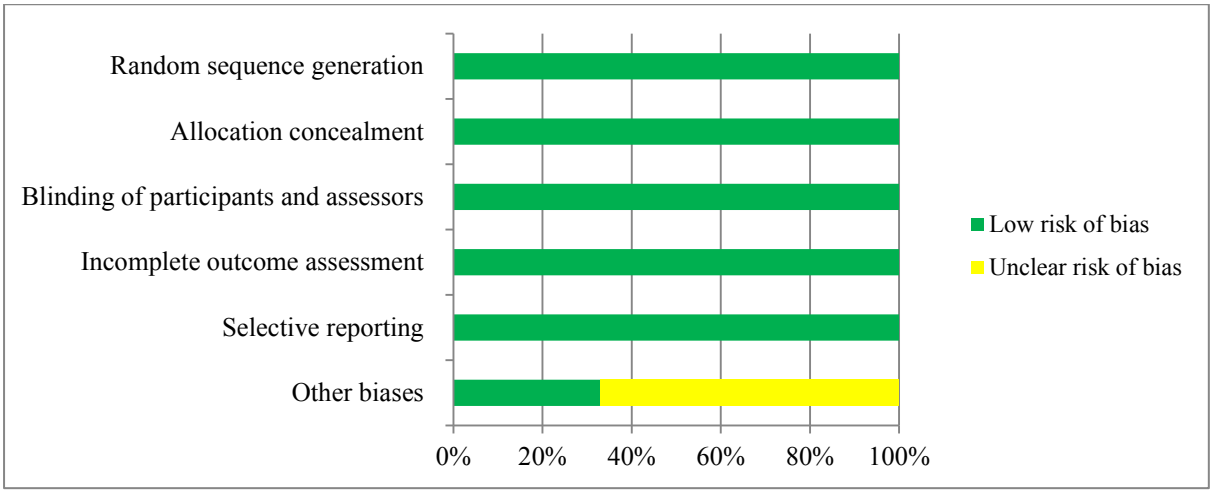


Table 2: Summary of methodological quality assessment: review authors' judgement about each methodological quality item for each study

Study	Quality assessment item								
	1	2	3	4	5	6	7	8	9
VISUAL I[4]	Y	Y	Y	Y	Y	Y	Y	Y	Y
VISUAL II[5]	Y	Y	Y	Y	Y	Y	Y	Y	Y
HURON[7]	Y	Y	Y	Y	Y	Y	Y	Y	Y

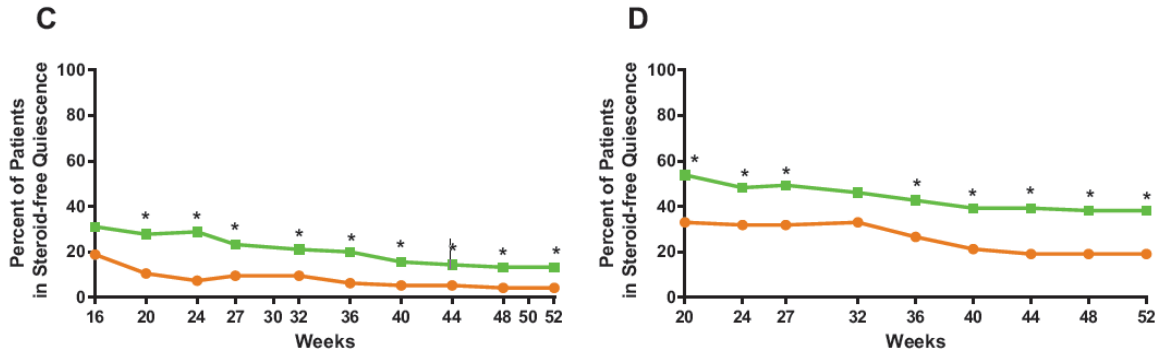
Y, yes (low risk of bias); N, no (high risk of bias); U, unclear (insufficient details to assess quality item)

1: Were participants assigned to study groups using an acceptable random method?
2: Was allocation concealment adequately conducted?
3: Were eligibility criteria specified for selecting participants?
4: Was the study adequately powered?
5: Were study groups comparable for most prognostic indicators at baseline?
6: Were patients and investigators/outcome assessors blinded to treatment allocation?
7: Was follow-up adequate (≥70% randomised patients analysed)?
8: Were reasons for attrition /exclusions stated ?
9: Was an intention-to-treat analysis included?

Feasibility of meta-analysis

It was not considered appropriate to meta-analyse the findings of the VISUAL I[4] and VISUAL II[5] studies because VISUAL I[4] enrolled patients with active uveitis and VISUAL II[5] enrolled patients with inactive uveitis. Active uveitis refers to current inflammation in the eye, whereas patients with inactive uveitis have limited inflammation, usually because of treatment with corticosteroids or immunosuppressants. In addition, the magnitude of the treatment effect is likely to be associated with the degree of disease activity and inflammation at baseline with patients with little inflammation or vision loss at baseline less likely to show an improvement in outcome. NMA was also not considered feasible or appropriate, for the reasons discussed in Section 5.2.3.

Figure 3: Proportion of patients with steroid-free quiescence in VISUAL I (C) and VISUAL II studies (D)



C: Week 16 was the first time-point for assessing steroid-free quiescence in VISUAL I because the mandatory steroid burst was tapered to zero by week 15.
D: Week 20 was the first time-point for assessing steroid-free quiescence in VISUAL II because the mandatory steroid burst was tapered to zero by week 19

Source: Landewee *et al.,* 2016[61]

Results for macular oedema

Measures of macular oedema were reported in terms of change in central macular thickness (CMT) for patients with MO at baseline and time to OCT evidence of MO in patients who developed the condition during the studies.

Macular oedema: VISUAL studies

In the VISUAL studies,[4, 5] ADA did not significantly reduce the time to OCT evidence of MO in the patients with active uveitis (HR 0.70; 95% CI 0.39 to 1.26; *p*=0.231) or in patients with inactive uveitis (HR 0.75; 95% CI 0.34 to 1.69; p=0.491). There was a significant difference in change in CMT in patients with active uveitis (VISUAL I,[4] *p*=0.020) but not in those with inactive uveitis (VISUAL II,[5] p = 0.451) (Table 3). Additional post-hoc analyses presented by the company for patients without macular hole and/or retinal detachment in VISUAL I showed that ADA resulted in statistically significant reductions in time to OCT evidence of macular oedema in at least one eye on or after week 6 (HR, 0.33; 95% CI 0.12 to 0.90; *p*=0.023) and the percentage change in CRT in each eye from best state achieved prior to week 6 to the final/ early termination visit (mean difference, -12.0; 95% CI -21.5 to -2.5, *p*=0.014).[56]

Macular oedema: HURON study

CMT was assessed by optical coherence tomography (OCT) at a number of study sites in HURON. Baseline mean central macular thickness was 344.0 (SD, 141.6) µm in 39 patients in the DEX 700 group) and 324.6 (SD,145.5) µm in 43 patients in the sham group. Mean difference for the decrease in

CMT between patients in the DEX 700 and sham arms was statistically significant at week 8 only (decrease -99.4 µm (SD, 151.8) versus -12.4 µm (SD, 123.7); *p*=0.004, Table 3) but not at week 26 (p=0.58).

Outcomes of incidence of MO are discussed further in Section 5.2.2.4 Safety of included interventions.

Table 3: Macular oedema outcomes in VISUAL I and VISUAL II

Macular oedema outcomes in VISUAL studies[4, 5]					
Time to macular oedema in ≤1 eye [median/ months (IQR)][a]	**ADA**		**Placebo**		Comparison between groups [HR (95%CI)]
VISUAL I [4] (active uveitis) Time frame: on or after week 6 (months)	11.1 (2.6 to 15.9) (n = 55 patients)		6.2 (1.4 to not estimable) (n = 45 patients)		0.70 (0.39 to 1.26); p=0.231
VISUAL II[5] (inactive uveitis) Time frame: on or after week 2 (months)	not estimable due to low number of events (n = 90 patients)		not estimable due to low number of events (n = 95 patients)		0.75 (0.34 to 1.69); p=0.491
Percentage change in macular thickness, µm (SD)	**ADA**		**Placebo**		Comparison between groups mean difference (95%CI)]
VISUAL I [4] (active uveitis)	Left eye	9.6 (29.76)	Left eye	20.2 (52.01)	- 11.4 (-20.9 to -1.8); p= 0.020[b]
	Right eye	8.2 (25.8)	Right eye	22.0 (62.48)	
	(n=101 patients)		(n=102 patients)		
VISUAL II[5] (inactive uveitis)	Left eye	4.5 (29.82)	Left eye	6.4 (20.67)	- 2.3 (-8.5 to 3.8); p=0.451
	Right eye	5.4 (34.83)	Right eye	7.7 (28.88)	
	(n=114 patients)		(n=107 patients)		

Macular oedema outcomes in HURON study[7]			
Decrease in macular thickness, µm (SD)	**DEX 700 (n =39 patients)**	**Sham (n=43 patients)**	**Comparison between groups [mean difference (95%CI)]**
Week 8	-99.4 (151.8)	-12.4 (123.7)	-87.0 (-147 to -27), p=0.004
Week 26	-50.2 (102.9)	-35.5 (134.9)	-14.7 (-66 to 37), p=0.58

ADA, adalimumab; CI, confidence interval; NR, not reported; SD, standard deviation,

[a] Comparison: Change from best state reached prior to week 6 to final or early termination[56]

5.2.2.4 Effectiveness data from non-randomised studies of dexamethasone

5.2.2.4.1 DEX studies

A summary of effectiveness data from 11 non-randomised, non-comparative studies of DEX 700 implant is shown in Appendix 5.[22, 49, 50, 64-71] This is based on data within the company submission for dexamethasone;[48] original study publications have not been examined due to time constraints. These data are included here as they provide some data on repeat implants, implants in both eyes and

corticosteroid reduction, which were not assessed in the HURON RCT. Non-randomised studies of ADA are not included here as they were not provided in the company submission and it was beyond the scope of this assessment to undertake a *de novo* review of these data.

Following a single implant, two studies reported significant improvements in BCVA at 2 to 3 months but a return to baseline values by 6 months,[22, 67] and significant improvements in VH up to 6 months,[22, 67] with a return to baseline by 12 months in the study with longer follow-up.[22] Significant improvements in CRT were reported up to 6 months after single implant in one study,[67] and up to 3 months in another study with a return to baseline by 6 months.[68]

Studies in which patients received between 1 and 4 implants reported improvements in BCVA at 12 months,[49, 68, 71] stated as significant in one study.[49] In studies with patients having a mix of single or multiple implants and macular oedema, significant improvements in CRT were reported up to 12 months in one study[49] while another study reported significant improvements at 3 months but not at 6 months.[70]

In terms of repeat implants, one study reported that after the second implant BCVA significantly improved by 1 month but then decreased, with a similar trend following up to 6 implants (not significant but small patient numbers).[22] CRT also showed a significant temporary improvement after the second implant with similar (non-significant) improvements after third and fourth implants, while VH showed a similar pattern.[22] Another study reported that the improvements in BCVA and CRT at 1 month were similar (not significantly different) following the first and second implants.[69]

The median time from first to second implant was 10 months in a study of uveitis patients,[49] while in four studies of uveitic macular oedema the mean/median time to second implant was 4.7, 5.0, 7.1 and 10 months.[50, 66, 68, 71] The mean time from second to third implant was 3.4 months in one study of uveitic macular oedema.[66]

Implants in both eyes were assessed in one study, in which 3/11 (27%) patients receiving implants in both eyes had a response (reduced CRT and improved BVCA) in the second eye.[22]

In terms of reduction in other therapies following a single implant, one study reported that 21/27 (78%) patients reduced or stopped systemic or local treatment,[22] while in another study 3/12 (25%) patients reduced their corticosteroid dose,[64] and in another study systemic corticosteroids were reduced or discontinued in 14/32 (44%) and discontinued in 8/32 (25%) at 6 months.[67] In studies using a mix of single or multiple implants, in one study 62% had reduction in systemic corticosteroids or

immunosuppressants and 36% had steroid discontinuation at 12 months,[49] while in another study systemic corticosteroids were reduced or discontinued in 78% and discontinued in 32% at 12 months.[50]

5.2.2.4.2ADA studies

Non-RCT data were presented in the company submission[56] and this was based on a retrospective audit presented in the Clinical Commissioning Policy for anti-TNF treatment options for adult patients with severe refractory uveitis.[72]. The study evaluated data for patients > 18 years with different clinical forms of uveitis receiving ADA (40 mg/2 week) or infliximab (3 to 5 mg/kg/2 weeks). The main findings of the audit were as follows:

- Clinical remission of uveitis was observed in all patients (n=41) on biologics; (mean (±SD) follow-up period =1.36 (±0.88) person years).
- 48.78% of patients experienced VA improvement; (mean ± SD follow-up of 2.51± 2.01 person years).
- Fewer patients (17.07%) had worsening of VA; (mean ± SD follow-up period =4.38 ± 3.50 person years,
- Patients receiving biologics, in due course, required less or reduced concomitant treatments.
  - 88.89% of patients showed reduction in steroid dose to ≤10 mg; (mean ± SD follow-up of 3.06 ± 2.32 person years)
  - 75.85% of patients showed reduction in steroid dose to ≤5 mg (mean ± SD follow-up of 3.15 ± 1.76 person years)
  - 45.16% of patients discontinued steroid treatment; (mean ± SD follow-up of 3.49 ± 1.59 person years)
  - 83.33% of patients showed reduction in the number and/or use of IMT: (mean ± SD follow-up of 1.54 ± 0.99 person years).
- Patient-reported outcomes reported in the audit[72] are summarised as follows:
  - A significant decrease in vision-related quality of life (VCM) was directly associated with decrease in visual acuity in the worse eye within 1 year of starting biologics (p=0.0064).
  - Median vision-related VCM scores decreased with increasing follow-up time from time of starting treatment with biologics.
  - Mean SF-36 PCS scores (<47) were lower than those of the general population. However, the SF-36 MCS scores (>47) were higher than estimates for the general population, with an exception of scores obtained at year 3(duration of audit period, not reported).

5.2.2.5 Safety of included interventions

Safety information from Summaries of Product Characteristics

The SmPC for the dexamethasone implant states that the most commonly-reported adverse events (AEs) are those frequently observed with ophthalmic steroid treatment or intravitreal injections, including: elevated intraocular pressure (IOP); cataract; and conjunctival or vitreal haemorrhage. Less frequently reported, but more serious, adverse reactions include endophthalmitis (severe eye infection), necrotizing retinitis (viral infection of the retina), retinal detachment and retinal tear.[6]

The SmPC for ADA summarises AEs from studies of 9,506 patients across a range of conditions. The SmPC states that the most commonly reported adverse reactions are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache and musculoskeletal pain. TNF-antagonists such as ADA affect the immune system and their use may affect the body's defence against infection and cancer. Fatal and life-threatening infections (including sepsis, opportunistic infections and tuberculosis), hepatitis B virus reactivation, and various malignancies (including leukaemia, lymphoma and hepatosplenic T-cell lymphoma) have also been reported with use of ADA. Serious haematological, neurological and autoimmune reactions have also been reported, including rare reports of pancytopenia, aplastic anaemia, central and peripheral demyelinating events and reports of lupus, lupus-related conditions and Stevens-Johnson syndrome.[3]

Safety data from pivotal RCTs

Safety data from the RCTs are based on the published journal articles for HURON[7] and VISUAL I and II,[4, 5] the company submissions [48, 56] and clinical study reports.[51, 55, 59] In the case of HURON, the safety data are based on all patients who were randomised to a group and received treatment: 76/77 (99%) for the DEX 700 group and 75/76 (99%) for the sham group. Within the 26-week trial, the mean exposure to the intervention was 25.9 weeks in both the DEX 700 and sham groups. For the two RCTs of ADA versus placebo, safety data included all randomised patients in both trials: n=111 (100%, ADA) and 112 (100%, placebo) in VISUAL I, and 115 (100%, ADA) and 114 (100%, placebo) in VISUAL II. It should be noted that in these trials, exposure to ADA was longer than exposure to placebo because treatment failure (and cessation of study treatment) occurred earlier; median exposure in VISUAL I was 19 weeks (ADA) versus 13 weeks (placebo), and in VISUAL II was 35 weeks (ADA) versus 22 weeks (placebo). Therefore, one may expect more events in the ADA than placebo groups.

A summary of adverse events (AEs) is provided in Table 4. An AE of any type occurred in 80% (DEX 700) versus 68% (sham) in HURON,[7] and in 85-91% (ADA) versus 79-84% (placebo) in the two VISUAL studies.[4, 5] Serious AEs occurred in 9% (DEX 700) versus 6.7% (sham) in HURON, and in 6-14% (ADA) versus 5-8% (placebo) in the VISUAL studies.[4, 58] There were no deaths in the HURON

study,[7] and one death in the ADA arms of each of the VISUAL studies;[4, 58] neither death was considered to be treatment-related.

Systemic AEs

Serious systemic AEs are shown in Table 5. Table 6 lists other systemic AEs which either a) occurred in at least 5% of patients in any treatment group (for HURON[7]), or b) occurred in at least 5% of patients in the ADA groups (for the VISUAL trials),[4, 73] and/or c) were noted as potentially important within uveitis treatments by clinical advisors to the AG. No reported systemic AEs (serious or non-serious) were substantially higher for DEX 700 compared with sham. Serious infections were higher for ADA than placebo in VISUAL I[4] (4.5% versus 1.8%) but not VISUAL II[5] (1.7% versus 1.8%). Malignancies and chronic renal failure each occurred in a total 3 patients across the ADA arms of both trials, versus no patients in the placebo arms. The majority of the listed systemic AEs were somewhat higher for ADA than placebo.

Immunogenicity

In VISUAL I,[4] anti-adalimumab antibodies were detected in 3/110 (2.7%) patients in the ADA group. These 3 patients had treatment failure at 16, 44 and 48 weeks (compared with a median time to treatment failure of 24 weeks among the remaining 107 patients).[4] In VISUAL II,[5] anti-adalimumab antibodies were detected in 6/115 (5%) patients in the ADA group. Five of these six patients had treatment failure at weeks 13, 16, 16, 24 and 31 (not estimable for the remaining patients).[5]

Ocular AEs

Ocular AEs are shown in Table 7. In terms of serious ocular AEs, endophthalmitis (severe eye infection) and severe uveitis worsening occurred in 1 patient each in the DEX 700 group versus none for placebo. Conjunctival haemorrhage occurred in 30% for DEX 700 versus 21% for sham, while rates were low in the VISUAL trials. Other ocular AEs are detailed in Table 7.

Raised IOP occurred in 25% for DEX 700 versus 7% for sham, while there was little difference between ADA and placebo. In the DEX 700 group, IOP ≥25 mmHg peaked at Week 3 (7.1% versus 1.4% placebo), while IOP ≥35 mmHg peaked at Week 12 (4.1% versus 0% placebo). By Week 26, no patients in the DEX 700 group had IOP ≥25 mmHg, versus 4.2% in the placebo group.

Glaucoma rates showed little difference between DEX 700 (0%) and sham (2.7%) in HURON or between ADA (0.9%) and placebo (0%) in VISUAL I.[4] In HURON, no patients required incisional surgery for glaucoma, while 2 patients (2.6%) in the DEX 700 group required laser iridotomies in the study eye for iris bombe and raised IOP. At any single time-point across the 26 weeks, up to 23% of

patients in the DEX 700 group required IOP-lowering medication (the percentage requiring this at any point in the study is not reported).

Cataracts occurring among eyes that were phakic (had a natural lens) at baseline were 9/62 (15%) for DEX 700 versus 4/55 (7%) for sham. Cataracts occurring among phakic eyes with no cataract at baseline were 9/42 (21%) for DEX 700 versus 4/28 (14%) for sham. For ADA, no data were reported on whether eyes were phakic or had cataract at baseline; cataracts occurring in all patients were higher for ADA than placebo in VISUAL I[4] (3.6% versus 1.8%) but higher for placebo in VISUAL II[5] (1.7% versus 5.3%). Cataract surgery among phakic eyes occurred in 1/62 (1.6%) for DEX 700 versus 2/55 (3.6%) for sham; in VISUAL II[5] cataract surgery occurred in 1 patient for ADA versus 2 patients for placebo.

Safety data from non-randomised studies of dexamethasone

A summary of safety data from 11 non-randomised, non-comparative studies of dexamethasone implant is shown in Appendix 6.[22, 49, 50, 64-71] This is based on data presented within the company submission for dexamethasone.[48] The proportion of patients with increased IOP is typically higher in real-world studies than in an RCT, which may reflect the inclusion of patients with prior need for IOP-lowering medications, who were excluded from HURON.[48] Implant migration to the AC has been reported in a few patients and occurred in eyes which were aphakic (no lens) or pseudophakic (artificial lens).[48] A few cases of endophthalmitis or retinal detachment were reported after administration of DEX 700.[48] Non-randomised studies of ADA are not included here as they were not provided in the company submission and it was beyond the scope of this assessment to undertake a *de novo* review of these data.

Table 4: Summary of adverse events in included RCTs

Trial	**HURON**		**VISUAL I[4](active uveitis)**		**VISUAL II[5] (inactive uveitis)**	
Intervention / comparator	**DEX implant 0.70mg**	**Sham**	**ADA, 40mg every 2wk**	**Placebo**	**ADA, 40mg every 2wk**	**Placebo**
Time over which AEs measured	26 wk (mean 25.9 wk)	26 wk (mean 25.9 wk)	≤80 wk (median 19 wk)	≤80 wk (median 13 wk)	≤80 wk (median 35 wk)	≤80 wk (median 22 wk)
AEs (all)	61/76 (80.3%)	51/75 (68.0%)	94/111 (84.7%)	88/112 (78.6%)	105/115 (91.3%)	96/114 (84.2%)
AEs considered possibly treatment-related	46/76 (60.5%)	21/75 (28.0%)	ADA-related: 45/111 (40.5%) Steroid-related: 57/111 (51.4%)	ADA-related: 35/112 (31.3%) Steroid-related: 53/112 (47.3%)	ADA-related: 64/115 (55.7%) Steroid-related: 50/115 (43.5%)	ADA-related: 52/114 (45.6%) Steroid-related: 48/114 (42.1%)
Serious AEs	7/76 (9.21%)	5/75 (6.7%)	15/111 (13.5%)	5/112 (4.5%)	7/115 (6.1%)	9/114 (7.9%)
Serious AEs considered possibly treatment-related	NR	NR	ADA-related: 6/111 (5.4%) Steroid-related: 2/111 (1.8%)	ADA-related: 2/112 (1.8%) Steroid-related: 2/112 (1.8%)	ADA-related: 2/115 (1.7%) Steroid-related: 0/115 (0%)	ADA-related: 2/114 (1.8%) Steroid-related: 3/114 (2.6%)
Discontinuations due to AEs	2/76 (2.6%)	0/75 (0%)	11/111 (9.9%)	4/112 (3.6%)	10/115 (8.7%)	7/114 (6.1%)

AE, adverse effect, wk, week

Table 5: Serious systemic adverse events (all those reported in RCTs)

Trial	HURON[7]		VISUAL I[4] (active uveitis)		VISUAL II (inactive uveitis)	
Intervention / comparator	**DEX implant 0.70mg**	**Sham**	**ADA, 40mg every 2wk**	**Placebo**	**ADA, 40mg every 2wk**	**Placebo**
Deaths	0/76 (0%)	0/75 (0%)	1/111 (0.9%) (not treatment-related)	0/112 (0%)	1/115 (0.9%) (not treatment-related)	0/114 (0%)
Hospitalisation	NR	NR	NR	NR	NR	NR
Infections (serious)	NR	NR	5/111 (4.5%)	2/112 (1.8%)	2/115 (1.7%)	2/114 (1.8%)
Tumours/malignancy	NR	NR	2/111 (1.8%)	0/112 (0%)	1/115 (0.9%)	0/114 (0%)
Anaphylactic reaction	NR	NR	1/111 (0.9%)	0/112 (0%)	NR	NR
Demyelinating disease	NR	NR	1/111 (0.9%)	0/112 (0%)	0/115 (0%)	0/114 (0%)
Renal failure, chronic	NR	NR	1/111 (0.9%)	0/112 (0%)	2/115 (1.7%)	0/114 (0%)
Accidental overdose	NR	NR	1/111 (0.9%)	0/112 (0%)	NR	NR
Ligament/tendon rupture	NR	NR	1/111 (0.9%)	0/112 (0%)	NR	NR
Fracture	NR	NR	0/111 (0%)	1/112 (0.9%)	1/115 (0.9%)	1/114 (0.9%)
Hepatitis, acute	NR	NR	0/111 (0%)	1/112 (0.9%)	NR	NR
Abortion induced	NR	NR	0/111 (0%)	1/112 (0.9%)	NR	NR
Neutropenia	NR	NR	NR	NR	1/115 (0.9%)	0/114 (0%)
Dysphagia (difficulty swallowing)	NR	NR	NR	NR	1/115 (0.9%)	0/114 (0%)
Dysarthria (unclear speech)	NR	NR	NR	NR	1/115 (0.9%)	0/114 (0%)
Status migrainosus	NR	NR	NR	NR	1/115 (0.9%)	0/114 (0%)
Epistaxis (nosebleed)	NR	NR	NR	NR	1/115 (0.9%)	0/114 (0%)
Pleurisy	NR	NR	NR	NR	1/115 (0.9%)	0/114 (0%)
Cardiac tamponade	NR	NR	NR	NR	1/115 (0.9%)	0/114 (0%)
Aortic dissection	NR	NR	NR	NR	1/115 (0.9%)	0/114 (0%)
Deep vein thrombosis	NR	NR	NR	NR	0/115 (0%)	2/114 (1.8%)
Hypertensive crisis	NR	NR	NR	NR	0/115 (0%)	1/114 (0.9%)
Arthritis	NR	NR	NR	NR	0/115 (0%)	1/114 (0.9%)
Cerebrovascular accident	1/76 (1.3%)	0/75 (0%)	NR	NR	NR	NR
Pelvic inflammatory disease	1/76 (1.3%)	0/75 (0%)	NR	NR	NR	NR
Cerebellar infarction	1/76 (1.3%)	0/75 (0%)	NR	NR	NR	NR
Pyelonephritis	0/76 (0%)	1/75 (1.3%)	NR	NR	NR	NR
Ankylosing spondylitis	0/76 (0%)	1/75 (1.3%)	NR	NR	NR	NR

Table 6: Systemic adverse events in RCTs

Trial	HURON[7]		VISUAL I[4] (active uveitis)		VISUAL II[5] (inactive uveitis)	
Intervention / comparator	**DEX 700**	**Sham**	**ADA, 40mg every 2wk**	**Placebo**	**ADA, 40mg every 2wk**	**Placebo**
Systemic AEs (≥5% in any group for DEX or ≥5% in treatment group for ADA)						
Nasopharyngitis	NR		21/111 (18.9%)	8/112 (7.1%)	18/115 (15.7%)	19/114 (16.7%)
Headache	5/76 (6.6%)	5/75 (6.7%)	12/111 (10.8%)	15/112 (13.4%)	17/115 (14.8%)	17/114 (14.9%)
Fatigue	0/76 (0%)	2/75 (2.7%)	12/111 (10.8%)	7/112 (6.3%)	14/115 (12.2%)	9/114 (7.9%)
Arthralgia (joint pain)	0/76 (0%)	2/75 (2.7%)	10/111 (9.0%)	11/112 (9.8%)	27/115 (23.5%)	12/114 (10.5%)
Back pain	NR	NR	9/111 (8.1%)	2/112 (1.8%)	9/115 (7.8%)	7/114 (6.1%)
Injection site reactions	NR	NR	7/111 (6.3%)	7/112 (6.3%)	23/115 (20.0%)	15/114 (13.2%)
Urinary tract infection	NR	NR	7/111 (6.3%)	0/112 (0%)	13/115 (11.3%)	10/114 (8.8%)
Cough	NR	NR	7/111 (6.3%)	4/112 (3.6%)	11/115 (9.6%)	6/114 (5.3%)
Bronchitis	NR	NR	7/111 (6.3%)	4/112 (3.6%)	NR	NR
Hyperhidrosis (increased sweating)	NR	NR	7/111 (6.3%)	3/112 (2.7%)	NR	NR
Muscle spasms	NR	NR	7/111 (6.3%)	4/112 (3.6%)	NR	NR
Nausea	0/76 (0%)	4/75 (5.3%)	6/111 (5.4%)	7/112 (6.3%)	2/115 (1.7%)	3/114 (2.6%)
Paraesthesia ("pins + needles")	NR	NR	6/111 (5.4%)	0/112 (0%)		
Insomnia	NR	NR	5/111 (4.5%)	8/112 (7.1%)	8/115 (7.0%)	3/114 (2.6%)
Myalgia (muscle pain)	NR	NR	5/111 (4.5%)	2/112 (1.8%)	6/115 (5.2%)	2/114 (1.8%)
Hypertension	2/76 (2.6%)	3/75 (4.0%)	4/111 (3.6%)	1/112 (0.9%)	7/115 (6.1%)	5/114 (4.4%)
Liver changes: Alanine aminotransferase increased	NR	NR	1/111 (0.9%)	2/112 (1.8%)	8/115 (7.0%)	1/114 (0.9%)
Liver changes: Aspartate aminotransferase increased	NR	NR	1/111 (0.9%)	1/112 (0.9%)	6/115 (5.2%)	1/114 (0.9%)
Pain in extremity	NR	NR	NR	NR	10/115 (8.7%)	3/114 (2.6%)
Upper respiratory tract infection	NR	NR	NR	NR	10/115 (8.7%)	3/114 (2.6%)
Injection site pain	NR	NR	NR	NR	8/115 (7.0%)	9/114 (7.9%)
Sinusitis	NR	NR	NR	NR	8/115 (7.0%)	4/114 (3.5%)
Additional systemic AEs (noted as potentially important by clinical advisors)						
Anxiety	NR	NR	5/111 (4.5%)	0/112 (0%)	5/115 (4.3%)	2/114 (1.8%)
Renal: Elevated creatinine	NR	NR	4/111 (3.6%)	2/112 (1.8%)	2/115 (1.7%)	3/114 (2.6%)
Weight gain	NR	NR	3/111 (2.7%)	2/112 (1.8%)	2/115 (1.7%)	0/114 (0%)
Anaemia	NR	NR	3/111 (2.7%)	0/112 (0%)	0/115 (0%)	2/114 (1.8%)

Trial	HURON[7]		VISUAL I[4] (active uveitis)		VISUAL II[5] (inactive uveitis)	
Intervention / comparator	**DEX 700**	**Sham**	**ADA, 40mg every 2wk**	**Placebo**	**ADA, 40mg every 2wk**	**Placebo**
Muscle weakness (myasthenia)	NR	NR	3/111 (2.7%)	0/112 (0%)	NR	NR
Cushing's syndrome	NR	NR	2/111 (1.8%)	1/112 (0.9%)	1/115 (0.9%)	0/114 (0%)
Depression	NR	NR	1/111 (0.9%)	1/112 (0.9%)	2/115 (1.7%)	3/114 (2.6%)
Diabetes	NR	NR	1/111 (0.9%)	2/112 (1.8%)	2/115 (1.7%)	0/114 (0%)
Osteoporosis	NR	NR	1/111 (0.9%)	1/112 (0.9%)	0/115 (0%)	2/114 (1.8%)

AE, adverse effect

Table 7: Ocular adverse events in RCTs

Trial	HURON[7]		VISUAL I[4] (active uveitis)		VISUAL II[5] (inactive uveitis)	
Intervention / comparator	**DEX 700**	**Sham**	**ADA, 40mg every 2wk**	**Placebo**	**ADA, 40mg every 2wk**	**Placebo**
Serious ocular AEs in study eye* (all reported in trials)						
Retinal detachment	2/76 (2.6%)	2/75 (2.7%)	1/111 (0.9%)	1/112 (0.9%)	0/115 (0%)	1/114 (0.9%)
Endophthalmitis (severe eye infection)	1/76 (1.3%)	0/75 (0%)	NR	NR	NR	NR
Uveitis worsening (as serious AE)	1/76 (1.3%)	0/75 (0%)	NR	NR	NR	NR
Cataract (as serious AE)	0/76 (0%)	1/75 (1.3%)	NR	NR	NR	NR
Choroidal neovascularisation	NR	NR	1/111 (0.9%)	0/112 (0%)	0/115 (0%)	1/114 (0.9%)
Transient blindness	NR	NR	NR	NR	1/115 (0.9%)	0/114 (0%)
Subretinal fluid	NR	NR	NR	NR	0/115 (0%)	1/114 (0.9%)
Ocular AEs in study eye* (≥5% in any group for DEX or ≥5% in treatment group for ADA)						
Raised IOP	19/76 (25.0%)	5/75 (6.7%)	3/111 (2.7%)	2/112 (1.8%)	3/115 (2.6%)	2/114 (1.8%)
IOP ≥25 mmHg	Wk 3: 5/70 (7.1%) Wk 8: 3/73 (4.1%) Wk 26: 0/74 (0%)	Wk 3: 1/70 (1.4%) Wk 8: 0/71 (0%) Wk 26: 3/72 (4.2%)	NR	NR	NR	NR
IOP ≥35 mmHg	Wk 3: 1/70 (1.4%) Wk 8: 2/73 (2.7%) Wk 26: 0/74 (0%)	Wk 3: 0/70 (0%) Wk 8: 0/71 (0%) Wk 26: 0/72 (0%)	NR	NR	NR	NR
Conjunctival haemorrhage	23/76 (30.3%)	16/75 (21.3%)	0/111 (0%)	1/112 (0.9%)	3/115 (2.6%)	2/114 (1.8%)
Vitreous haemorrhage	NR	NR	Eye haemorrhage: 1/111 (0.9%) Retinal haemorrhage: 1/111 (0.9%)	Eye haemorrhage: 0/112 (0%) Retinal haemorrhage: 2/112 (1.8%)	1/115 (0.9%)	0/114 (0%)
Ocular discomfort	10/76 (13.2%)	6/75 (8.0%)				
Eye pain	9/76 (11.8%)	10/75 (13.3%)	9/111 (8.1%)	2/112 (1.8%)	9/115 (7.8%)	6/114 (5.3%)
Cataract - Of all patients - Of phakic eyes at baseline - Of phakic eyes with no cataract at baseline	 9/76 (11.8%) 9/62 (14.5%) 9/42 (21.4%)	 4/75 (5.3%) 4/55 (7.3%) 4/28 (14.3%)	 4/111 (3.6%) NR NR	 2/112 (1.8%) NR NR	 2/115 (1.7%) NR NR	 6/114 (5.3%) NR NR
Iridocyclitis	7/76 (9.2%)	4/75 (5.3%)	1/111 (0.9%)	0/112 (0%)	3/115 (2.6%)	2/114 (1.8%)
Ocular hypertension	6/76 (7.9%)	0/75 (0%)	3/111 (2.7%)	1/112 (0.9%)	0/115 (0%)	2/114 (1.8%)

Trial	HURON[7]		VISUAL I[4] (active uveitis)		VISUAL II[5] (inactive uveitis)	
Intervention / comparator	**DEX 700**	**Sham**	**ADA, 40mg every 2wk**	**Placebo**	**ADA, 40mg every 2wk**	**Placebo**
Myodesopsia (floaters or vitreal cells)	6/76 (7.9%)	5/75 (6.7%)	NR	NR	NR	NR
Uveitis / uveitis worsening	6/76 (7.9%)	7/75 (9.3%)	11/111 (9.9%)	8/112 (7.1%)	6/115 (5.2%)	9/114 (7.9%)
Conjunctival hyperaemia (red eye)	5/76 (6.6%)	7/75 (9.3%)	NR	NR	NR	NR
Vision blurred	5/76 (6.6%)	3/75 (4.0%)	8/111 (7.2%)	2/112 (1.8%)	NR	NR
Macular oedema	3/76 (3.9%)	6/75 (8.0%)	NR	NR	7/115 (6.1%)	7/114 (6.1%)
Eye pruritis (itching)	3/76 (3.9%)	5/75 (6.7%)	NR	NR		
Visual acuity reduced	1/76 (1.3%)	4/75 (5.3%)	NR	NR	6/115 (5.2%)	10/114 (8.8%)
Eye swelling	1/76 (1.3%)	4/75 (5.3%)	NR	NR	NR	NR
Conjunctivitis	0/76 (0%)	4/75 (5.3%)	NR	NR	NR	NR
Additional ocular AEs in study eye* (noted as potentially important by clinical advisors)						
Cataract surgery - Of all patients - Of phakic eyes at baseline - Of phakic eyes with no cataract at baseline	 1/76 (1.3%) 1/62 (1.6%) 1/42 (2.4%)	 2/75 (2.7%) 2/55 (3.6%) 2/28 (7.1%)	NR	NR	 1/115 (0.9%) NR NR	 2/114 (1.8%) NR NR
IOP-lowering medications	Up to 16/71 (23%) at any single time-point	NR, presumed 0%	NR	NR	NR	NR
IOP-lowering surgery - Incisional surgery, laser trabeculoplasty, cryotherapy - Laser iridotomy	 0/76 (0%) 2/76 (2.6%)	 0/75 (0%) 0/75 (0%)	NR	NR	NR	NR
Glaucoma	0/76 (0%)	2/75 (2.7%)	1/111 (0.9%)	0/112 (0%)	NR	NR
Low IOP (hypotony)	1/76 (1.3%)	0/75 (0%)	NR	NR	NR	NR

*Study eye relates to the Dex study (HURON) where one eye was designated the study eye

AE, adverse effect; IOP, intra-ocular pressure

5.2.2.6 Ongoing studies

Ongoing studies relevant to the Decision Problem are shown in Table 8. These were identified via a search of the ClinicalTrials.gov database (for terms for uveitis plus adalimumab or dexamethasone) and from the dexamethasone company submission.[48]

Ongoing studies of DEX 700

Two ongoing RCTs of DEX 700 were identified, both in patients with macular oedema due to uveitis. Both compare against other local treatments. The POINT trial (NCT02374060, due to complete 2018) compares DEX 700 versus intravitreal triamcinolone or periocular triamcinolone, while the MERIT trial (NCT02623426, due to complete 2019) compares DEX 700 versus intravitreal methotrexate or intravitreal ranibizumab. In addition, a long-term safety cohort study of DEX 700 (NCT01539577) in 875 patients with posterior segment-involving uveitis or central or branch retinal vein occlusion (CRVO or BRVO) was due to complete in March 2016, but no published results were identified.

Ongoing studies of ADA

Three ongoing RCTs of ADA were identified. One small RCT (the ADUR trial, NCT00348153)[74] compared ADA plus corticosteroids and immunosuppressants versus corticosteroids in combination with immunosuppressants, and was due to be completed in March 2013. This is potentially of interest due to its active comparator arm. However, no published results were identified other than an abstract reporting intermediate results for 20 of 25 patients; this was not included in the clinical effectiveness section due to the limited results presented.[74] Two further RCTs of ADA are due to complete in 2019. The RUBI trial (NCT02929251) aims to compare ADA against two further biologic therapies: anakinra (an interleukin-1 receptor antagonist) and tocilizumab (an antibody against the interleukin-6 receptor). The IVAS trial (NCT02706704) compares subcutaneous ADA against intravitreal ADA.

In addition, a non-randomised extension study of ADA (VISUAL III, M11-327, NCT01148225) enrolled patients from the VISUAL I and VISUAL II studies (ADA or placebo arms) who either completed these trials or experienced treatment failure. Patients who discontinued VISUAL I or II due to treatment failure were defined as having active disease at VISUAL III entry, while patients who completed VISUAL I or II had inactive disease. They received open-label ADA (40mg every other week) and were followed up for 78 weeks (active uveitis patients) or 54 weeks (inactive uveitis patients). The completion date is 2018. Preliminary data are available from a conference abstract.[75] This states that of 243 patients with active uveitis after 78 weeks, 96.3% had no new inflammatory lesions relative to week-8, 91.0% had AC cell grade ≤0.5+, and 87.8% had VH grade ≤0.5+. Of 128 patients with inactive uveitis after 54 weeks, 98.5% had no new inflammatory lesions relative to baseline, 98.5% had AC cell grade ≤0.5+, and 92.6% had VH grade ≤0.5+. Mean systemic corticosteroid daily dose decreased from 12.7 to 3.68 prednisone equivalents by year 1 for patients with active uveitis and

remained stable from 1.48 to 1.21 prednisone equivalents for inactive patients. Adverse events rates were stated to be comparable to the VISUAL I and VISUALII trials, but no data were presented in terms of number of patients with events. No data were presented for visual acuity or VFQ-25.

Table 8: Ongoing studies

Study name Company	Type N est.	Population	Interventions	Key outcomes	Follow-up	Start and end dates	Reference
DEX 700							
PeriOcular and INTravitreal Corticosteroids for Uveitic Macular Edema Trial (POINT) JHSPH Center for Clinical Trials / National Eye Institute (NEI)	RCT 267	- Non-infectious anterior, intermediate, posterior or panuveitis - Active or inactive - Macular oedema	- DEX 700 - Intravitreal triamcinolone 4 mg - Periocular triamcinolone 40 mg	- Change in CRT - IOP elevation - Change in BCVA	8 and 24 weeks	March 2015 to July 2018	ClinicalTrials.gov [NCT02374060]
Macular Edema Ranibizumab v. Intravitreal Anti-inflammatory Therapy Trial (MERIT) JHSPH Center for Clinical Trials / National Eye Institute (NEI)	RCT 240	- Non-infectious anterior, intermediate, posterior or panuveitis - Inactive or minimally active - Macular oedema	- DEX 700 - Intravitreal methotrexate 400 µg - Intravitreal ranibizumab 0.5 mg	- Change in CRT	8 weeks and 6 months	Nov 2016 to March 2019	ClinicalTrials.gov [NCT02623426]
A Long-Term Safety Study of Ozurdex in Clinical Practice Allergan	Cohort 875	- Central or branch retinal vein occlusion (CRVO or BRVO) or non-infectious posterior segment-involving uveitis - Macular oedema	- DEX 700	- Adverse events	2 years	Mar 2012 to Mar 2016 (CSR available Sept 2016*)	ClinicalTrials.gov [NCT01539577]
ADA							
Adalimumab in Uveitis Refractory to Conventional Therapy (ADUR Trial) Heidelberg University / Abbott	RCT 25	- Non-infectious uveitis - Active despite ≥7.5mg/d corticosteroids	- Adalimumab 40mg every other week + corticosteroids + immunosuppressants - Corticosteroids + immunosuppressants	- % BCVA improved ≥3 lines EDTRS - Inflammatory activity - Cystoid macula edema - Cumulative steroid dosage	Up to 24 weeks	Aug 2006 to March 2013	ClinicalTrials.gov [NCT00348153] Abstract: Mackensen 2012[74]
Randomized Trial Comparing Efficacy of Adalimumab, Anakinra and Tocilizumab in Non-infectious Refractory Uveitis (RUBI) Assistance Publique - Hôpitaux de Paris	RCT 120	- Non-infectious intermediate, posterior, or pan-uveitis - Active	- Adalimumab 40mg every other week - Anakinra 100 mg/day - Tocilizumab 162 mg/week	- % ≥2-step reduction in VH or AC cells - Change in VH - Change in BCVA - Change in CRT - Change in steroid dose	16 weeks	Oct 2016 to May 2019	ClinicalTrials.gov [NCT02929251]

Study name **Company**	**Type** **N est.**	**Population**	**Interventions**	**Key outcomes**	**Follow-up**	**Start and end dates**	**Reference**
Intravitreal Adalimumab Versus Subcutaneous Adalimumab in Non-infectious Uveitis (IVAS)	RCT 32	- Non-infectious intermediate, posterior, or pan-uveitis - Active	- Adalimumab (subcutaneous) 40mg every other week - Adalimumab (intravitreal), 1.5 mg/ 0.03 mL every 4 weeks	- Change in VH - Change in AC score - Change in BCVA (ETDRS, logMAR) - Change in CRT - Success in steroid tapering	26 weeks	Feb 2016 to June 2019	ClinicalTrials.gov [NCT02706704]
A Study of the Long-term Safety and Efficacy of Adalimumab in Subjects With Intermediate-, Posterior-, or Pan-uveitis (VISUAL III) AbbVie (previously Abbott)	Non-RCT 400	- Non-infectious intermediate, posterior, or pan-uveitis - Active or inactive patients from VISUAL I and VISUAL II (completed or experienced treatment failure)	- Adalimumab 40mg every other week	- Adverse events - BCVA, new lesions, VH, AC cells, CRT, VFQ-25, reduction in immunosuppression (active and inactive pts separately)	Up to 330 weeks (6.3 years)	Nov 2010 to Mar 2018	ClinicalTrials.gov [NCT01148225] Abstract Suhler 2016[75]

*Allergan submission

AC, anterior chamber; BCVA, best-corrected visual acuity; CRT, central retinal thickness; EDTRS, Early Treatment Diabetic Retinopathy Study; IOP, intra-ocular pressure; logMAR, logarithm of the Minimum Angle of Resolution; N est, Number of patients estimated; RCT, randomised controlled trial; VFQ-25, Visual Functioning Questionnaire-25; VH, vitreous haze

5.2.3 Indirect comparison of treatments: rationale for not undertaking

The Decision Problem states that relevant comparators include: periocular or intravitreal corticosteroid injections; intravitreal corticosteroid implants; systemic corticosteroids; systemic immunosuppressants; TNF-alpha inhibitors; and intravitreal methotrexate. The trials of DEX 700 and ADA only compared these interventions to placebo/sham. In the absence of direct evidence comparing ADA and DEX 700, and the absence of direct evidence comparing either of these treatments to a comparator reflective of current UK practice, an indirect comparison using an NMA was considered. An NMA allows a simultaneous comparison between interventions based on a synthesis of any direct and indirect evidence about treatment effects across RCTs that share at least one treatment in common with at least one other study.

5.2.3.1 Consideration of indirect comparison for all studies of clinically relevant comparators

RCTs which included any of the treatments in the comparator decision set for posterior segment-involving uveitis were sought. In addition to the one of DEX 700 (HURON)[7] and two of ADA (VISUAL I and II),[4, 5] 13 additional trials of relevant comparators were identified,[35, 36, 76-86] as shown in Table 9.

Unfortunately, it was considered infeasible and inappropriate to conduct an NMA for the reasons outlined in Table 9. However, a brief summary of all identified trials of relevant comparators is provided in this section for information: study characteristics in Table 10 and a summary of reported outcomes in Table 11. Reasons for not including the additional identified trials in the NMA included the following:

1) No link to the network containing ADA and DEX 700 i.e. no common comparator: this applies to studies of fluocinolone implant,[76, 77] periocular steroids,[79] methotrexate[35, 86] and mycophenolate mofetil.[35] The use of elicitation of experts' belief to inform the parameters required to link disconnected networks was considered in depth but was not implemented for two reasons. It was deemed to be infeasible in the time frame and, moreover, would be of questionable benefit given the concerns related to the comparability of the two main trials (see Section 5.2.3.2) and hence the validity of the resulting connected network.
2) Heterogeneity in patient populations in terms of active/inactive uveitis: It was not considered appropriate to pool studies of patients with active and inactive uveitis. Active uveitis refers to current inflammation in the eye, whereas patients with inactive uveitis have limited inflammation, usually due to treatment with corticosteroids or immunosuppressants. The treatment effect is likely to be related to the degree of

activity/inflammation at baseline. The trial of etanercept,[80] one trial of ADA (VISUAL II),[5] and one trial of voclosporin[84, 85] could not be analysed with the HURON[7] and VISUAL I[4] studies for this reason. In terms of trials in patients with inactive uveitis, the trials of etanercept[80] and voclosporin[84, 85] had no comparable outcome data in order to conduct an NMA with VISUAL II.[5]

3) Heterogeneity in patient populations for other reasons: The trial of intravitreal triamcinolone[78] was in patients who all had uveitic macular oedema (UMO), whereas in most trials only a subset had UMO. The treatment effect is likely to be associated with the proportion of patients with UMO at baseline because UMO causes vision loss. Therefore, treating UMO is likely to lead to greater gains in vision than treating patients with uveitis but no UMO. The trial of azathioprine[81] was in patients who all had Behcet's disease, whereas most trials were in a mixed population with only a small percentage having Behcet's and other systemic diseases; again, this is a clinically very different population. In addition, as noted in Section 5.2.3.2, there are many differences in populations and prior and concomitant treatments between the DEX 700 (HURON[7]) and ADA (VISUAL I[4]) studies for active uveitis.
4) Lack of comparable outcomes. Within the trials that had a common comparator with DEX 700 or ADA (i.e. a placebo arm),[78, 80-82, 84, 85] none reported outcomes consistent with those in the DEX 700 and ADA trials (outcomes summarised in Table 11). Change in VFQ-25 was reported for both HURON[7] and VISUAL I[4] but an NMA was not considered appropriate for the reasons listed in Section 5.2.3.2.

Table 9: Studies considered for network meta-analysis: Rationale for non-inclusion

Trial name /ref	**HURON**[7, 60]	**VISUAL I**[4]	**VISUAL II**[5]	**MUST**[76]	**Pavesio 2010**[77]	**Shin 2015**[78]	**Ferrante 2000**[79]	**Foster 2003**[80]
Intervention	**Dex implant** (LOCAL STEROID)	**ADA** (ANTI-TNF)	**ADA** (ANTI-TNF)	**Fluo implant** (LOCAL STEROID)	**Fluo implant** (LOCAL STEROID)	**Triam intravit inj.** (LOCAL STEROID)	**Triam perioc inj.** (LOCAL STEROID)	**Etanercept** (ANTI-TNF)
Comparator	**Placebo** (sham)	**Placebo**	**Placebo**	**Steroids & immuno.**	**Steroids & immuno.**	**Placebo** (sham)	**M-pred perioc inj.**	**Placebo**
Reasons for non-inclusion in NMA	• Outcomes measured from baseline (different to VISUAL)	• Outcomes measured from peak after steroid burst to treatment failure (not from randomisation as in HURON)	• Inactive uveitis • Outcomes measured from baseline	• Not connected to network	• Not connected to network	• 100% uveitic macular oedema • No data on VA, VH, VFQ-25	• Not connected to network	• Inactive uveitis • No comparable VA outcomes • No data on VH or VFQ-25
Trial name / ref	**Yazici 1990**[81]	**Murphy 2005**[36]	**de Vries 1990**[82]	**Nussenblatt 1991**[83]	**Bodaghi 2012 (Active)**[84, 85]	**Bodaghi 2012 (Maintenance)**[84, 85]	**Mackensen 2013**[86]	**Rathinam 2004**[35]
Intervention	**Azathioprine** (IMMUNOSUPP.)	**Cyclosporine** (IMMUNOSUPP.)	**Cyclosporine** (IMMUNOSUPP.)	**Cyclosporine** (IMMUNOSUPP.)	**Voclosporin** (IMMUNOSUPP.)	**Voclosporin** (IMMUNOSUPP.)	**Methotrexate** (IMMUNOSUPP.)	**Methotrexate** (IMMUNOSUPP.)
Comparator	**Placebo**	**Tacrolimus**	**Placebo**	**Prednisolone**	**Placebo**	**Placebo**	**Interferon-β**	**Mycophen. mofetil**
Reasons for non-inclusion in NMA	• 100% Behcet's disease • No clear data on VA, VH, VFQ-25	• Only connected via study of cyclosporine versus sham (de Vries 1990) which has no data on VA, VH, VFQ-25	• No data on VA, VH, VFQ-25	• Only connected via study of cyclosporine versus sham (de Vries 1990) which has no data on VA, VH, VFQ-25	• No data on VA, VH, VFQ-25	• Inactive uveitis • No data on VA, VH, VFQ-25	• Not connected to network	• Not connected to network

Anti-TNF, anti-tumour necrosis factor; immunosupp, immunosuppressant; NMA, network meta-analysis; VA, visual acuity; VFQ-25, Visual Functioning Questionnaire-25; VH, vitreous haze

Table 10: Studies considered for network meta-analysis: Study characteristics

Trial name Author, year	HURON[7, 60]	VISUAL I[4]	VISUAL II[5]	MUST[76]	Pavesio 2010[77]	Shin 2015[78]	Ferrante 2000[79]	Foster 2003[80]
Intervention	**DEX 700**	**ADA** (40mg every 2wk)	**ADA** (40mg every 2wk)	**Fluocinolone implant** (0.59mg)	**Fluocinolone implant** (0.59mg)	**Triamcinolone intravitreal inject.**	**Triamcinolone periocular injection**	**Etanercept** (25mg SC twice/wk)
Comparator	**Placebo** (sham)	**Placebo**	**Placebo**	**Systemic steroids & immunosuppressant**	**Systemic steroids & immunosuppressant**	**Placebo** (sham)	**Methylprednisolone periocular inject.**	**Placebo**
N pts randomised	153 (DEX 700+sham)	223	229	255	140	50	36	20
Age: inc, mean (rnge)	≥18, 45 (18 to 82)	≥18, 43 (18 to 81)	≥18, 43 (NR)	≥13, 46 (NR)	≥6, 42 (12-75)	≥20, 52 (NR)	NR, NR (NR)	≥18, 47 (NR)
Location of uveitis	Int/post	Int/post/pan	Int/post/pan	Int/post/pan	Int/post/pan	NR	Int/post	NR
Duration uveitis (mo)	Dex 51, Sham 61	Ada 40, Pbo 51	61	Fluo 47, Control 43	NR	NR	NR	NR (6mo MTX)
Bilateral uveitis (%)	NR	91%	96%	88%	NR	NR	NR	NR
% with MO	NR	36% left; 37% right	NR	41%	NR	100%	NR	NR
Systemic conditions	No uncontrolled systemic condition	None 73%, sarcoid 8%, Behcet's 7%, VKH 12%	None 56%, sarcoid 16%, Behcet's 6%, Other 8%	None 73%, systemic 27%; none requiring systemic therapy	None requiring systemic therapy	None 48%, systemic 52% (sarcoid, Behcet's, VKH)	NR	None 60%, SLE 15%, HLA-B27 15%, arthritis 10%
Current inflammation (active, non-active)	Active	Active	Inactive (≥28 days)	Active (or recently active)	Inactive ("clinically quiet")	NR	Active (vitritis or UMO)	Inactive
Inclusion criteria: visual acuity and inflammation	- VH ≥1.5 - BCVA 10-75 letters	At least one of: - VH ≥2 - AC cell grade ≥2 - Inflammatory lesions	- VH ≤0.5 - AC cell grade ≤0.5 - No inflammatory lesions - Steroid dependent	- No VH criteria (some had VH=0) - BCVA = hand motions or better	- VH ≤2 - AC cells ≤10 - Visual acuity ≥1.4 logMAR (6/150)	- Uveitic macular oedema - BCVA 25 to 80 EDTRS letters	- Uveitic macular oedema or vitritis	NR
% prior HD steroids / immunosuppressants	26% steroids or imm.	100% HD steroids	100% HD steroids; some imm.	Some steroids; some imm. (% NR)	100% HD steroids; some imm.	100% HD steroids; some imm.	NR	100% methotrexate (imm.)
Concomitant treatment	- 26% stable dose steroids or imm. - Rescue: local steroids, systemic meds (new or incr)	- All: Prednisone 60mg/d, tapered by wk 15 - Some imm, max 1	- All: Prednisone 10-35mg/d tapered by wk 19 - Some: imm, max 1	- Fluo arm: Steroids & imm discont. - Control arm: Steroids (tapered), imm (86%)	- Fluo arm: Steroids & imm discont. - Control arm: HD steroids +/- imm - Rescue: steroids	All: Systemic steroids or imm and topical steroids	NR	All: Methotrexate (tapered); steroid eyedrops if needed
Which eyes treated	One (right if bilat.)	N/A (systemic)	N/A (systemic)	Both if bilateral	One (worse if bilat.)	One (worse if bilat.)	NR (assume one)	N/A (systemic)
Which eyes analysed	Study eye only	Left & right sep.	Left & right sep.	All uveitic eyes	Study eye only	Study eye only	NR (study eye?)	Both eyes, all pts
Duration: treatment & follow-up	Single implant Follow-up 6 months (26 wk)	Up to 80 wk (1.5yr) Ada: 19 wk [med] Pbo: 13 wk [med]	Up to 80 wk (1.5yr) Ada: 35 wk [med] Pbo: 22 wks [med]	Repeat if recurred Follow-up 2 years	Single implant Follow-up 2 years	Repeat if MO recurred Follow-up 6 months	Repeat at 6 wk if needed Follow up 3 months	6 months (24 weeks)

(cont.)

Trial name Author, year	Yazici 1990[81]	Murphy 2005[36]	de Vries 1990[82]	Nussenblatt 1991[83]	Bodaghi 2012 (Active)[84, 85]	Bodaghi 2012 (Maintenance)[84, 85]	Mackensen 2013[86]	Rathinam 2004[35]
Intervention	**Azathioprine** (2.5mg/kg daily)	**Cyclosporine** (2.5-5.0mg/kg daily)	**Cyclosporine** (10mg/kg/d)	**Cyclosporine** (10mg/kg/d, oral)	**Voclosporin** (0.2, 0.4, 0.6 mg/kg BID)	**Voclosporin** (0.2, 0.4, 0.6 mg/kg BID)	**Methotrexate** (20mg SC weekly)	**Methotrexate** (25mg oral weekly)
Comparator	**Placebo**	**Tacrolimus** 0.03-0.08mg/kg (daily)	**Placebo**	**Prednisolone** (42-64mg/d, oral)	**Placebo**	**Placebo**	**Interferon-β**(44ug SC 3 times weekly)	**Mycophenolate mofetil** (1g twice/d)
N pts randomised	48	37	27	56	218	232	19	80
Age: inc, mean (rnge)	Any age, 32 (NR)	NR, med 43 (NR)	≥18, 45 (22-75)	≥10, 38 (10-61)	≥13, med 42 (NR)	≥13, med 43 (NR)	≥18, med 42 (NR)	≥16, 39 (NR)
Location of uveitis	NR	Int/post/pan	Int/post/pan	Int/post	Int/post/pan	Int/post/pan	Intermediate	Int/post/pan
Duration uveitis (mo)	Aza 103, Pbo 83	12-24	Cyclo 67, Pbo 78	NR	52	52	≥1 yr	NR
Bilateral uveitis (%)	71%	76%	NR	100%	NR	NR	NR	81%
% with MO	NR	NR	NR	55%	NR	NR	100%	41%
Systemic conditions	Behcet's 100%	None 70%, Behcet's 11%, sarcoidosis 8%	None 74%, Behcet's 15%, sarcoidosis 11%	None 82%, sarcoidosis 13%, VKH 5%	NR	NR	None 74%, multiple sclerosis 26%	None 35.5%, VKH 54%, Behcet's 8%, sarcoidosis 2.5%
Current inflammation (active, non-active)	NR	NR	Active	Active	Active	Inactive	Active	Active
Inclusion criteria: visual acuity and inflammation	NR	NR	- BCVA ≤0.5 in best eye (or Behcet's or trauma)	- VA 20/40 or worse, both eyes - Inflammation (VH, VA decrease, retinal lesions)	- VH ≥2	NR	- Uveitic macular oedema (≥250um) - Visual acuity ≤20/30 (0.2 logMAR)	At least one of: - VH ≥1 - AC cell grade ≥1 - Vitreous cells ≥1 - Active lesions
% prior HD steroids / immunosuppressants	No steroids or imm. (past month)	100% HD steroids (or required)	100% HD steroids	No steroids or imm. (past month)	100% HD steroids (or contra/refused)	100% HD steroids	100% HD steroids and acetazolamide	100% HD steroids
Concomitant treatment	Rescue: Systemic steroids if required	Some: Oral steroids only	All: Oral steroids (tapered)	No systemic treatments; topical meds permitted	Some: Oral steroids	Some: Oral steroids	NR	All: Oral steroids (tapered) Some: Topical steroid
Which eyes treated	N/A (systemic)	N/A (systemic)	N/A (systemic)	N/A (systemic)	N/A (systemic)	N/A (systemic)	N/A (systemic)	N/A (systemic)
Which eyes analysed	Both? (unclear)	Per patient	Unclear	Per patient	Study eye or either	Study eye or either	Study eye (worse)	All uveitic eyes
Duration: treatment & follow-up	2 years	3 months	Up to 1 year	3 months	6 months (24 wk)	6 months (26 wk)	3 months	6 months

AC, anterior chamber; aza, azathioprine; BCVA, best-corrected visual acuity; bilat, bilateral; cyclo, cyclosporine; EDTRS, Early Treatment Diabetic Retinopathy Study; fluo, fluocinolone; HD, high-dose; HLA-B27, human leukocyte antigen B27; imm, immunosuppressants; int, intermediate; logMAR, logarithm of the Minimum Angle of Resolution; med, median; mo, months; MO, macular oedema; MTX, methotrexate; N, number; N/A, not applicable; NR, not reported; pan, panuveitis; Pbo, placebo; post, posterior; sep, separately; SLE, systemic lupus erythematosus; UMO, uveitic macular oedema; VA, visual acuity; VH, vitreous haze; VKH, Vogt-Koyanagi-Harada disease; wk, weeks; yr, years

Table 11: Studies considered for network meta-analysis: Outcomes reported

Trial name /ref	HURON[7, 60]	VISUAL I[4]	VISUAL II[5]	MUST[76]	Pavesio 2010[77]	Shin 2015[78]	Ferrante 2000[79]	Foster 2003[80]
Intervention	**Dex implant**	**ADA**	**ADA**	**Fluo implant**	**Fluo implant**	**Triam intravit inj.**	**Triam perioc inj.**	**Etanercept**
Comparator	**Placebo** (sham)	**Placebo**	**Placebo**	**Steroids & immuno.**	**Steroids & immuno.**	**Placebo** (sham)	**M-pred perioc inj.**	**Placebo**
Visual acuity								
VA final value		Y (logMAR)	Y (logMAR)	Y (ETDRS): 6, 2,24m		(No data just p=NS)		
VA change	Y (ETDRS): 6m	Y (logMAR)	Y (logMAR)	Y (ETDRS): 6,12,24m				
% improved ≥3 lines	Y: 2, 6mo			Y: 24 mo	Y: 24 mo			
% improved ≥2 lines	Y: 2, 6mo						Y	Y
Inflammatory activity								
VH: final	Y (final, no SD)	Y (final & change)	Y (change)					
% VH = 0	Y	Y		Y				
% VH improved ≥1	Y							
% VH improved ≥2	Y			(HR only)				
AC cell grade: change		Y	Y					
Complications								
Cataract: Incidence	Y	Y	Y	Y	Y	Y		
Cataract: % surgery	Y		Y	Y	Y	Y		
MO incidence	Y	Y		Y				
Time to MO		Y	Y					
Macular thick: change	Y	Y	Y			(no data, p-value)		
% eyes MO improved					Y (improved)			
Steroid reduction								
% reduced steroids						Y (% reduced)		
% rescue steroids	Y (intravit/systemic)						Y (intravitreal)	
Composite outcomes								
Time to treatment failure (active uveitis)		Y (worse AC cells; VH; VA; lesions)						
Uveitis recurrence			Y: AC; VH; VA; lesion		Y (AC; VH; VA)			Y (uveitis flare-ups)
Composite (positive)								
HRQoL								
Generic HRQoL		EQ5D, HADS, WPAI		Y (EQ-5D, SF-36)				
VFQ-25 comp: final	Y: 2, 4, 6m	Y		Y: 6, 12, 24m				
VFQ-25 comp: chge	Y (no SD/SE): 2, 6m	Y	Y	Y: 6, 12, 24m				
Adverse effects								
Systemic AEs	Y	Y	Y	Y	Y			Y
Ocular AEs	Y	Y	Y	Y	Y	Y	Y	

(cont.)

Trial name / ref	Yazici 1990[81]	Murphy 2005[36]	de Vries 1990[82]	Nussenblatt 1991[83]	Bodaghi 2012 (Active)[84, 85]	Bodaghi 2012 (Maintenance)[84, 85]	Mackensen 2013[86]	Rathinam 2004[35]
Intervention	**Azathioprine**	**Cyclosporine**	**Cyclosporine**	**Cyclosporine**	**Voclosporin**	**Voclosporin**	**Methotrexate**	**Methotrexate**
Comparator	**Placebo**	**Tacrolimus**	**Placebo**	**Prednisolone**	**Placebo**	**Placebo**	**Interferon-β**	**Mycophen. mofetil**
Visual acuity								
VA final value							Y (Snellen, logMAR)	
VA change	(unclear data)		(Landolt C, p-value)				Y (ETDRS, logMAR)	Y (logMAR)
% improved ≥3 lines				Y				
% improved ≥2 lines		Y					Y	
Inflammatory activity								
VH: final					(unclear data)		Y (final)	
% VH = 0								
% VH improved ≥1								
% VH improved ≥2				Y				
AC cell grade: change				Y			Y	
Complications								
Cataract: Incidence								Y
Cataract: % surgery								
MO incidence								
Time to MO								
Macular thick: change							Y	
% eyes MO improved				Y (resolved)			Y improved/resolved	Y (resolved)
Steroid reduction								
% reduced steroids			Y (% stopped)					
% rescue steroids	Y (intravenous)							
Composite outcomes								
Time to failure, active								
Uveitis recurrence		Y (prev responders)				Y (recurrence)		
Composite (positive)		Y: VA ≥2 lines or ophthalmoscopy=0	(no data, p-value)	Y (VA ≥3 lines or VH improvement ≥2)				Y: % steroid-sparing control inflammation
HRQoL								
Generic HRQoL							(SF-36. no data)	
VFQ-25 comp: final							Y	
VFQ-25 comp: chge								
Adverse effects								
Systemic AEs	Y	Y	Y	Y			Y	Y
Ocular AEs							Y	Y

Trial name / ref	Yazici 1990[81]	Murphy 2005[36]	de Vries 1990[82]	Nussenblatt 1991[83]	Bodaghi 2012 (Active)[84, 85]	Bodaghi 2012 (Maintenance)[84, 85]	Mackensen 2013[86]	Rathinam 2004[35]
Intervention	**Azathioprine**	**Cyclosporine**	**Cyclosporine**	**Cyclosporine**	**Voclosporin**	**Voclosporin**	**Methotrexate**	**Methotrexate**
Comparator	**Placebo**	**Tacrolimus**	**Placebo**	**Prednisolone**	**Placebo**	**Placebo**	**Interferon-β**	**Mycophen. mofetil**

AC, anterior chamber; AE, adverse effect; EDTRS, Early Treatment Diabetic Retinopathy Study; EQ5D, EuroQol-5D; fluo, fluocinolone; HADS, Hospital Anxiety and Depression Scale; HR, hazard ratio; HRQoL, health-related quality of life; immuno, immunosuppressants; logMAR, logarithm of the Minimum Angle of Resolution; mo, months; MO, macular oedema; M-pred, methylprednisolone; mycophen. mofetil, mycophenolate mofetil; VFQ-25, National Eye Institute Visual Functioning Questionnaire; NS, not significant; SD, standard deviation; SE, standard error; SF-36, Short Form-36; Triam, triamcinolone; VA, visual acuity; VH, vitreous haze; WPAI, Work Productivity and Activity Impairment questionnaire; Y, yes (reported)

5.2.3.2 Consideration of indirect comparison for trials of ADA and dexamethasone

The outcomes reported vary from trial to trial (see Section 5.2.2.1) and so the potential networks of evidence were considered separately for each outcome of interest. Outcomes considered for the NMA were VFQ-25, visual acuity, VH and adverse events. This was driven by the potential to undertake a NMA for these outcomes.

Two networks of evidence were considered. A diagram of Network 1 is provided in

Figure 4. Network 1 consists of two trials (HURON[7] and VISUAL I[4]) and allows pairwise comparison to be made between ADA, DEX 700 and placebo/sham (the common comparator of the two trials). The trials share common assessment time points at 8, 16 and 26/27 weeks (26 weeks for HURON[7] and 27 weeks for VISUAL I[4]). Given that HURON[7] is a 26 week trial comparison beyond this time point is not possible based on the observed data.

A diagram of Network 2 is provided in

Figure 5. Network 2 is an extension of Network 1, including the Multicenter Uveitis Steroid Treatment (MUST) trial of fluocinolone corticosteroid implant versus systemic corticosteroids and immunosuppressants under the assumption that the efficacy of the fluocinolone implant is the same as that of DEX 700. This allows an indirect comparison to systemic corticosteroids and immunosuppressants which may be considered more reflective of current UK practice than placebo/sham. An indirect comparison using this network is only possible at 26 weeks (the first follow up in the MUST trial).

Figure 4: Network 1 for VFQ-25 outcome. Indirect comparison of adalimumab, dexamethasone and placebo/sham.

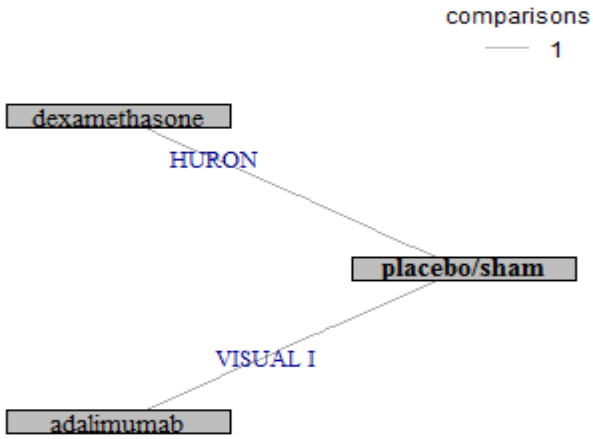
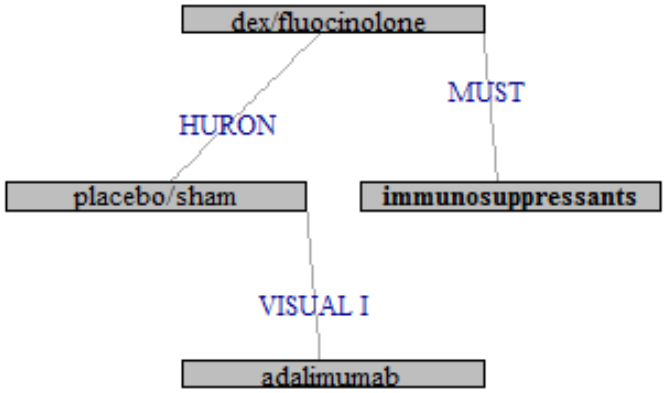


Figure 5: Network 2 for VFQ-25 outcome. Indirect comparison of adalimumab, dexamethasone, placebo/sham and immunosuppressants.



The AG began with a question about the best way to compare the treatment options within a network, with the prior belief that such an analysis could be undertaken. However, after substantial deliberation between all members of the AG and with the clinical advisors, it was reluctantly decided that an NMA was inappropriate and may provide misleading results. The main issues are listed below.

- **Baseline systemic therapy**

  In HURON, only 26% of patients were receiving systemic therapy at baseline whereas in VISUAL I[4], all patients were receiving systemic high-dose corticosteroids. Therefore, patients in these studies may have been at different "lines" of treatment. In addition, in VISUAL I[4], 91% of patients had bilateral uveitis, whereas the corresponding proportion is not reported in the case of HURON;[7] this may be a further difference in the patient populations in these studies.

- **Rescue therapy**

  A greater proportion of patients in the sham arm in HURON[7] received rescue therapy than in the DEX 700 arm (38.2% versus 22.1%). In VISUAL I[4], there was no reported difference in concomitant therapy between the two arms. It may be misleading to attribute an indirect effect of ADA versus DEX 700 to these interventions alone.

- **Comparability of the baseline treatments in HURON[7] and VISUAL I.[4]**

  VISUAL I included an initial steroid burst that was not included in HURON.[7] Thus, the baseline interventions are different and it would only be meaningful to combine the treatment effects across studies if the initial steroid burst did not affect the treatment effect. However, clinical advice suggests that the treatment effect will depend on the initial steroid burst. Patients experience an initial improvement from the steroid bust and there is less scope during this period for patients to demonstrate further improvement (i.e. effect of ADA is not additive to

the effect of the steroids). In the analyses undertaken by the company this issue is addressed by considering the "change from peak within first 6 weeks to final/termination visit" for each individual. This approach was not considered appropriate for estimating treatment effect because patients are only comparable at baseline and treatment effects should be estimated relative to baseline.

- **Validity of comparable efficacy assumption for dexamethasone and fluocinolone (Network 2 only).**
  Although DEX 700 and fluocinolone are both corticosteroid intravitreal implants, they cannot be considered clinically equivalent because the fluocinolone implant has higher potency (median duration of effect 30 months)[87] compared to the DEX 700 implant (median duration of effect of 6 months).[48] There are no head-to-head trials comparing DEX 700 and fluocinolone implants.

- **Issues with the reported data.**
  Patients in VISUAL I[4] were followed up to the time of treatment failure only and missing data beyond this point was imputed using LOCF. No other methods for dealing with missing data were considered and it is it is possible that the use of LOCF may provide a biased estimate of treatment effect since it assumes that the data is missing at random, which is not true in this case. Although LOCF was also used in the HURON[7] trial the issue is less problematic in this case because most patients were followed up for 26 weeks and treatment could not be discontinued (because the implants are not removed). Estimates of treatment effect for secondary outcomes (including VFQ-25, EQ-5D, visual acuity, VH) may be biased because data is only collected until treatment failure.

Evidence about key outcome measures could be synthesised using either absolute values at each time point or change from baseline. The use of absolute values was ruled out because of differences in response at baseline between the sham and treatment arms in HURON[7] for VFQ-25 (see **Error! Reference source not found.**). The sham arm has a higher mean VFQ-25 at baseline, whereas clinical advice suggests that the lower mean VFQ-25 associated with the treatment arm is likely to be more representative of the population. It was not possible account appropriately for baseline differences.

- **Treatment with adalimumab and dexamethasone is generally for different patient groups**
  As discussed in Section 3.3, there is only a small patient group in which it would be appropriate to compare DEX 700 and ADA, the most likely group being patients with bilateral uveitis with a temporary flare up. Consequently, an analysis that assumes that clinicians would be prepared to treat any patient in the population with any of the treatments is inappropriate.

Summary of clinical effectiveness and safety (RCTs)

Three RCTs were included in the review of clinical effectiveness; a summary of results is provided in **Error! Reference source not found.**. Two RCTs compared ADA versus placebo, for up to 80 weeks or until treatment failure, in patients with intermediate, posterior or panuveitis on high-dose oral corticosteroids: VISUAL I[4] (active uveitis) and VISUAL II[5] (inactive uveitis). Oral corticosteroids were tapered from baseline, and patients could receive up to one systemic immunosuppressant. One RCT (HURON[7]) compared DEX 700 (single 0.7mg implant) versus sham over 26 weeks' follow-up, in patients with intermediate or posterior uveitis. At baseline 25% were on systemic therapies which could be continued at a stable dose.[7] Thirteen additional studies of clinically-relevant comparator treatments (versus placebo or one another) were identified. However, due to clinical heterogeneity, differences in outcomes and lack of common comparators, it was not feasible to undertake a NMA. Therefore, the summary of clinical efficacy evidence presented here is restricted to the VISUAL I,[4] VISUAL II,[5] and HURON[7] studies.

Treatment failure in the VISUAL studies of ADA was defined as worsening of any of the following in either eye: AC cell grade; VH grade; BCVA, or new inflammatory lesions. In VISUAL I[4] (active uveitis), median time to treatment failure was 5.6 months for ADA compared to 3 months for placebo (hazard ratio (HR) 0.50 (95% CI 0.36 to 0.70, $p<0.001$). Treatment failure was experienced by 54.5% on ADA versus 78.5% on placebo. In VISUAL II[5] (inactive uveitis), median time to treatment failure was not estimable for ADA and 8.3 months for placebo; HR 0.57 (95% CI 0.39 to 0.84, $p=0.004$). Treatment failure was experienced by 39% on ADA versus 55% on placebo. In VISUAL I,[4, 51] there were significant benefits for ADA versus placebo for changes in the following (averaged across both eyes): visual acuity ($p=0.003$), inflammation (VH, $p<0.001$ and AC cell grade, $p=0.011$), macular oedema (change in central retinal thickness, $p=0.020$), VFQ-25 composite score ($p=0.010$) and EQ-5D ($p=0.044$). In VISUAL II,[5, 55] differences were not significant for ADA versus placebo for changes in any of the following (averaged across both eyes): visual acuity ($p=0.096$), inflammation (VH, $p<0.070$ and AC cell grade, $p=0.218$), macular oedema (change in central retinal thickness, $p=0.451$) VFQ-25 composite score ($p=0.160$) or EQ-5D ($p=0.836$).

In the HURON study,[7] there were significant benefits for DEX 700 versus sham for the following (measured in the study eye only): percentage of patients with VH score of zero at 8 weeks ($p<0.001$) and 26 weeks ($p=0.014$); percentage of patients with VH improvement ≥2 units at 8 weeks ($p<0.001$) and 26 weeks ($p=0.001$); percentage of patients with BCVA improvement of ≥3 lines over weeks 3 to 26 ($p<0.001$); mean BCVA improvement over weeks 3 to 26 ($p\leq0.002$); central retinal thickness at 8 weeks ($p\leq0.004$) though not at 26 weeks ($p\geq0.227$); change in VFQ-25 composite score (per patient as opposed to study eye) at 8 weeks ($p=0.007$) and 26 weeks ($p=0.001$), and; percentage of patients with

≥5-point improvement in VFQ-25 score at 8 weeks (p<0.001) and 26 weeks (p<0.05). Rescue medications (corticosteroid injections in the study eye or new/increased systemic corticosteroids or immunosuppressants) were required in 22% in the DEX 700 arm versus 38% for sham (p=0.030).

Since ADA affects the immune system, potential risks include infections and malignancy.[3] Serious infections were higher for ADA than placebo in VISUAL I[4] (4.5% versus 1.8%) but not VISUAL II[5] (1.7% versus 1.8%). Malignancies and chronic renal failure each occurred in a total of 3 patients across both trials (ADA) versus none (placebo). Systemic AEs which were higher for ADA than placebo in at least one of the VISUAL studies[4, 5] included infections, injection site reactions, fatigue, arthralgia, myalgia, paraesthesia, hypertension and liver enzyme increases. Anti-adalimumab antibodies in patients on ADA occurred in 2.7% in VISUAL I[4] and 5% in VISUAL II.[5] There was little difference between ADA and placebo in rates of ocular AEs.

In terms of safety, risks for DEX 700 include those associated with intraocular steroids i.e. increased intraocular pressure (IOP), cataract and glaucoma, as well as infection and bleeding.[6] In the HURON study,[7] raised IOP occurred in 25% (DEX 700) versus 7% (sham), while IOP ≥25 mmHg occurred in 7.1% (DEX 700) versus 1.4% (sham). Glaucoma rates were lower for DEX 700 (0%) than sham (2.7%); no patients required incisional surgery for glaucoma, while 2.6% (DEX 700 group) required laser iridotomies, and at any single time-point up to 23% in the DEX 700 group required IOP-lowering medication (not reported for sham). Cataracts in eyes that were phakic (had a natural lens) at baseline occurred in15% (DEX 700) versus 7% (sham), and cataract surgery in 1.6% (DEX 700) versus 3.6% (sham). Endophthalmitis (severe eye infection) and severe uveitis worsening occurred in 1 patient each (DEX 700) versus none for sham. Conjunctival haemorrhage occurred in 30% (DEX 700) versus 21% (sham). No systemic adverse effects (AEs) were substantially higher for DEX 700 than sham.

	Adalimumab	Dexamethasone
	et al.[24]	
Treatment following remission	For all patients, treatment will continue until treatment failure	For all patients, treatment will continue until treatment failure
LCP(H): Limited current practice based on HURON; LCP(VI): Limited current practice based on VISUAL I; LCP(VII): Limited current practice based on VISUAL II		

Due to the substantial uncertainties associated with the above assumptions due to the limited evidence base, most of these are altered within exploratory analyses to test their impact upon the model results.

6.2.1.1 Model description

Patient population

The model population consists of people with non-infectious intermediate, posterior or pan uveitis. Patients receiving dexamethasone are assumed to have active disease, whilst the model assessed the cost-effectiveness of adalimumab separately for patients with active and inactive disease. An analysis was undertaken to explore the cost-effectiveness of dexamethasone use in one eye in patients with unilateral disease as a separate subgroup; the trial did not provide data separately for this group and hence it is considered to be exploratory. Owing to the lack of evidence, it was not possible to explore additional subgroups. A cohort of uveitis patients are assumed to enter the model with a mean age of 44.8, based on the mean age within HURON, [7] and are followed over a lifetime. The model population is limited to adults aged 18 years and over because the marketing authorisations for the technologies being considered relate only to this group.

Interventions

The two technologies considered were adalimumab (40mg every two weeks until treatment failure) and the dexamethasone implant (0.7mg, once only in the base case).

Within the clinical trials of adalimumab (VISUAL I[4] and II[5]), patients were already receiving high-dose corticosteroids at randomisation, plus a corticosteroid burst was given to all patients at the start of the VISUAL I trial; corticosteroids were tapered to zero by week 15 (VISUAL I) or week 19 (VISUAL II). Clinical advisors to the AG suggest that this is also likely to reflect clinical practice, although the SmPC suggests that adalimumab may be given alongside corticosteroids or alone.[3] Given the evidence available, for patients with active disease, the model considers the cost-effectiveness of adalimumab plus an initial oral corticosteroid burst, rather than adalimumab alone.

The dexamethasone implant can be administered in the affected eye to unilateral patients, in one eye for patients with bilateral disease, or in both eyes at staggered intervals for patients with bilateral disease. Patients could also receive more than one consecutive implant. Clinical advisors to the AG

whether patients had unilateral or bilateral disease was not recorded. Based upon the patient level data provided by Allergan, the proportion of patients with VH that was greater than zero in the non-study eye was 51%; clinical advisors to the AG stated that this suggests that at least 51% of patients had bilateral disease. Within the HURON trial, where patients had bilateral uveitis, the right eye was chosen for treatment.7 This resulted in the better-seeing eye being treated in 10.7% and 17.1% of cases for DEX 700 and sham respectively.

Given that the presence of unilateral or bilateral uveitis is not reported in HURON,7 it is not possible for the AG to undertake robust subgroup analysis around this factor. The base case model is therefore dependent on the assumption that the patients included within the HURON trial and the way in which dexamethasone is used within the trial would be representative of its use in practice. It is not possible to make robust conclusions about the subgroups separately in terms of cost-effectiveness; however an exploratory subgroup analysis has been undertaken (see Section 6.2.1.4). As described within Section 3.1, it is expected that around 70-80% of this patient population would have bilateral disease. However, it may be that because dexamethasone is a local treatment, patients with unilateral disease are more likely to be selected for dexamethasone both within the trial and in practice. Given that patients with bilateral disease have a greater capacity to benefit from treatment due to the BCVA of the better-seeing eye being the best predictor of quality of life, and treatment in one eye would cost the same whether given to a person with unilateral or bilateral disease, if the trial has a lower proportion of bilateral cases than in practice, then the effectiveness of dexamethasone may be underestimated. Conversely, if the trial has a higher proportion of bilateral cases than in practice, then the effectiveness of dexamethasone may be overestimated.

Time horizon

The time horizon of the model is the lifetime of patients (up to age 100 years) and a starting age of 44.8 years was used, representing the average age of patients with non-infectious posterior segment-involving uveitis within the HURON trial.[4, 5, 7] A time cycle of two weeks was chosen owing to this being the time between administration of adalimumab doses and when patients would also be assessed for disease progression. This is also a sufficiently short time cycle to capture all relevant clinical events associated with dexamethasone and current practice.

Discounting

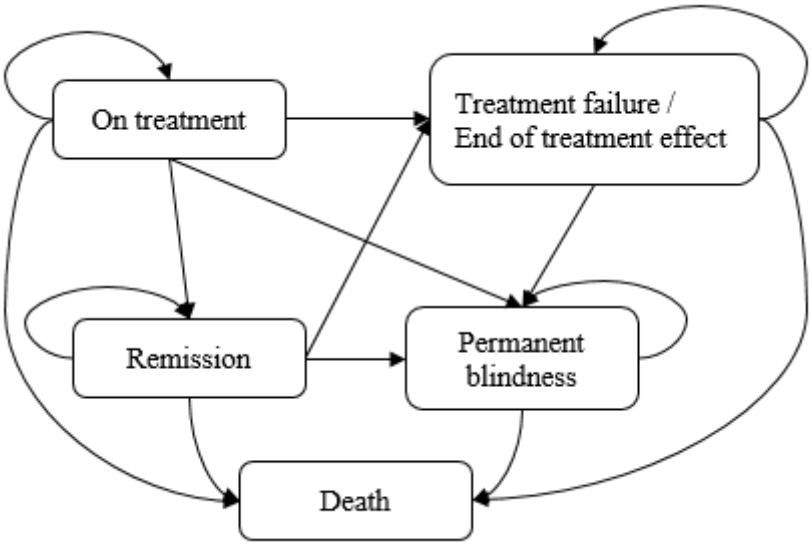
All costs and QALYs are discounted at a rate of 3.5% per year.

6.2.1.2 Model structure

The structure of the AG model is presented in Figure 6. The model includes five health states: (i) treatment: no permanent blindness; (ii) treatment failure: no permanent blindness; (iii) permanent

blindness; (iv) remission (no treatment); and (v) death. For dexamethasone, treatment is one implant which is assumed to be effective for six months, at which time patients will move to the treatment failure health state if they have remained in the treatment state until this time. Patients in the LCP(H) group begin in the 'treatment failure' state. Patients may discontinue adalimumab due to treatment failure, defined by the VISUAL trial criteria,[4, 5] at which time they will move to the second health state if they have remained in the treatment state until this time. Patients in the LCP(VI) and LLCP(VII) groups also begin in the treatment state and move to 'treatment failure' once they have met this criteria. Within the treatment state, HRQoL (defined by VFQ-25 or EQ-5D) could be improved due to the treatment effect or due to a reduction in adverse events. Treatment may also reduce the risk of experiencing permanent damage to the eye, resulting in a decreased risk of permanent legal blindness. Once a patient experiences legal blindness in the model, they can either remain in this health state or progress to death. Patients may also enter remission, whereby they do not receive further treatment, but they maintain the benefit of the previous treatment. Within the base case, the proportion of patients experiencing remission is assumed to be zero; however, the impact of increasing this proportion is considered within the exploratory analyses. An analysis was undertaken to explore the cost-effectiveness of dexamethasone use in one eye in patients with unilateral disease as a separate subgroup; the trial did not provide data separately for this group and hence it is considered to be exploratory. Owing to the lack of evidence, it was not possible to explore additional subgroups.

Figure 6: State transition diagram of the decision model



6.2.1.3 Estimation of model parameters

Treatment discontinuation

of life impacts associated with adverse events during the period in which the treatment is provided. The incidence of AEs from the trials was therefore used to calculate only the additional costs associated with their management. As such, adverse events included within the model are limited to those where the cost of treatment is substantial. Based upon advice from the clinical experts to the AG, adverse events associated with substantial costs of treatment are: cataract, raised IOP, glaucoma, serious infections; hypertension; fractures; and diabetes.

The probabilities for AEs per cycle (are shown in Table 12) were calculated based on the incidence in the trials and the mean follow-up time of each trial.

Table 12: Probability of AEs per cycle

			Active uveitis		**Inactive uveitis**		
	DEX 700	**LCP(H)**	**ADA**	**LCP(VI)**	**ADA**	**LCP(VII)**	**SS&I**
Raised IOP	0.019	0.005	0.002	0.002	0.001	0.001	0.001
Cataract	0.016	0.011	0.002	0.002	0.001	0.003	0.008
Glaucoma	0.000	0.002	0.001	0.000	0.000	0.000	0.001
Hypertension	0.002	0.003	0.002	0.001	0.003	0.003	0.002
Serious infections	0.000	0.000	0.003	0.003	0.001	0.001	0.000
Fracture	0.000	0.000	0.000	0.001	0.000	0.001	0.002
Diabetes	0.000	0.000	0.001	0.001	0.001	0.000	0.001

DEX 700: Dexamethasone 0.7mg; ADA: Adalimumab; SS&I: Systemic steroids and immunosuppressants: LCP(H): Limited current practice based on HURON; LCP(VI): Limited current practice based on VISUAL I; LCP(VII): Limited current practice based on VISUAL II; IOP: Intraocular pressure

Quality of life

Estimating the relationship between VFQ-25 and EQ-5D

The AG considered the published studies for mapping VFQ-25 to EQ-5D included in the database of mapping studies by Dakin.[105] However, none of the published mapping studies were based on a uveitis population, and considering that the AG had access to the VFQ-25 and EQ-5D patient-level data at baseline of the HURON study, the AG decided to fit a new mapping model. The AG used the approach that produced the best fit according to Browne et al.[106] (ordinary least squares) and it noticed that the mapping resulted in similar coefficient values to those presented by Payakachat et al.[107] which used an alternative modelling method (censored least absolute deviation). The mapping is used for all the analyses involving dexamethasone, within the exploratory analyses comparing the interventions with current practice as provided in MUST,[76] and within a sensitivity analysis for adalimumab.

The patient-level data from HURON were used to test for a correlation between VFQ-25 and EQ-5D at baseline. The scatter plot is presented in

Figure 7. A linear regression model was fitted to the data to predict EQ-5D utilities from the VFQ-25. One regression model was fitted to all three arms of the HURON trial; sham, dexamethasone implant 0.35mg; dexamethasone implant 0.7mg, in order to maximise the sample size for the regression analysis. The underlying assumption was that the relationship between VFQ-25 and EQ-5D utility would be independent of treatment. The fitted regression used in the economic model is:

$$EQ\text{-}5D\ utility = 0.4454059 + VFQ\text{-}25\ score * 0.0051322$$

It is recognised that a linear model is not bounded and is likely to have poor performance for utility values at the extremes. However, given that the mapping is only used for means, no extremes values are used. Alternative non-linear models (eg. quadratic regression) were also tested but did not significantly improve the fit to the data. The variance-covariance matrix of the slope and the intercept of the regression model is presented in

Table 13. To represent the uncertainty of the regression model, the matrix was used to sample the two coefficients of the regression model in the PSA.

Figure 7: The relationship between VFQ-25 and EQ-5D based on patient-level data from the HURON trial

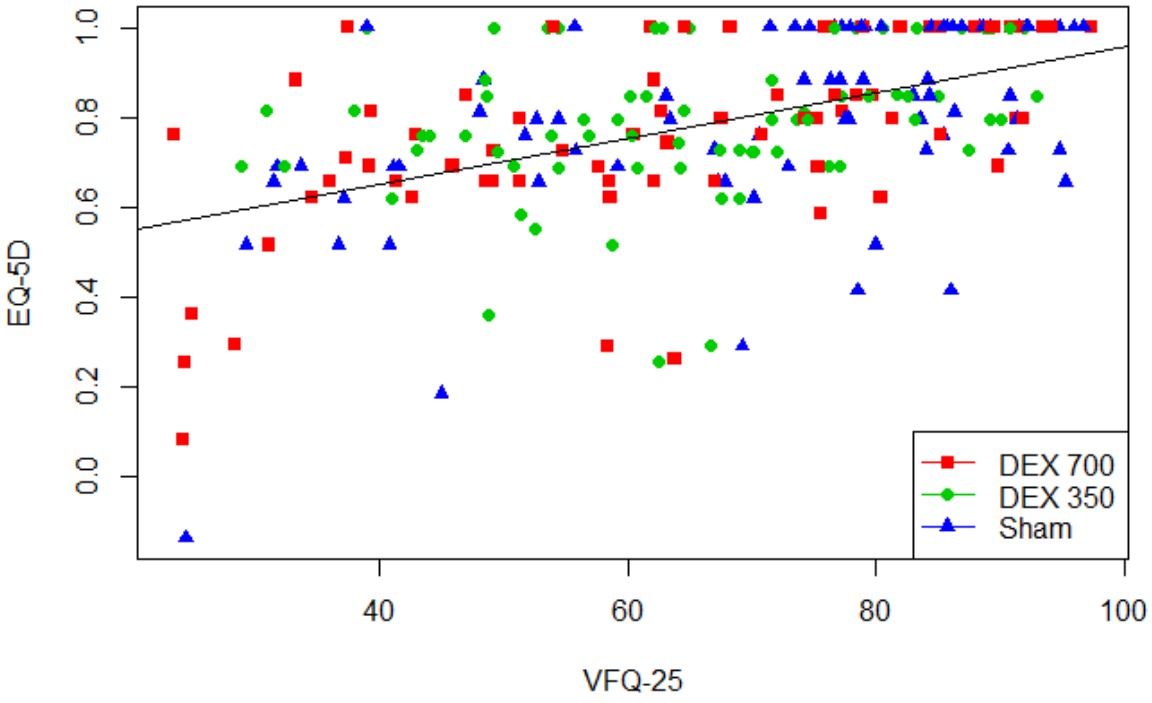


Table 13: Variance-covariance matrix of the intercept and the covariate of the regression model

Intercept	1.75E-03	
VFQ	-2.42E-05	3.63E-07
	Intercept	**VFQ**

The baseline utilities, i.e. the utilities for patients at week 0, were estimated based upon the patient level data from each trial: HURON[7] for dexamethasone and its comparator (LCP(H)), VISUAL I for adalimumab and its comparator in active patients (LCP(VI)), and VISUAL II in for adalimumab and its comparator in inactive patients (LCP(VII)).[4, 5] In HURON, the baseline utilities and visual acuity were substantially different between the sham and the dexamethasone arms (visual acuity was 71.3 for the sham arm and 63.7 for the DEX 700 arm). Clinical advisors to the AG were asked to consider whether the baseline difference in both utility and visual acuity are reasonably due to random variation. All three experts agreed that a difference in visual acuity of 10 letters or more is considered to be clinically significant and could be due to random variation below this level, and therefore it is plausible that the differences at baseline were due to random variation. The baseline utilities were not varied to represent any population subgroups because these data were not available from the trials. The impact of changing the baseline utility has been assessed within the univariate sensitivity analysis; however, this analysis assumes that the relative treatment effect remains the same. This is unlikely to be the case for subgroups with differing baseline utilities such as patients with unilateral or bilateral uveitis. However, there is no evidence from the trials around outcomes for these subgroups which would enable a robust subgroup analysis.

Estimating utility over time

VFQ-25 data from each follow-up point within the HURON trial[7] (weeks 0, 8, 16, 26) and EQ-5D data from each follow-up point of the VISUAL trials[4, 5] (weeks 0, 1, 4, 6, 8, 12, 16, 20, 24, 27, 32, then every four weeks until week 80) were used to estimate the change in utility for each treatment group over the time period of the trials. These were adjusted according to the average baseline utilities but maintaining the change from baseline in each arm.

When comparing adalimumab with its comparator, for patients who fail and hence discontinue treatment, it was assumed that utility returns to the baseline utility score, adjusted for any reduction in utility associated with age. For patients who receive adalimumab beyond the duration of the trial (80 weeks), it was assumed that their utility remains constant after the last follow-up point until treatment discontinuation. This utility is based on the mean of the last six months of data (see **Error! Reference source not found.** and **Error! Reference source not found.**). When comparing dexamethasone with

its comparator, the AG assumed that the utility of patients who received dexamethasone would drop to that of its comparator after the duration of the treatment effect. Within the base case analysis, the treatment effect was assumed to be 30 weeks long (four weeks longer than the trial period). Within the sensitivity analyses, the utility is assumed to decrease to the baseline utility score over varying time periods.

Error! Reference source not found., **Error! Reference source not found.** and **Error! Reference source not found.** present the predicted mean utility values over time, excluding any adjustments for blindness, for dexamethasone versus LCP(H) for active patients, adalimumab versus LCP(VI) for active patients, and adalimumab versus LCP(VII) for inactive patients, respectively.

Age adjustments to utility were based on the regression equation reported by Ara and Brazier.[96] Age-related utility was calculated using the following formula:

$$Utility = A \times (Male) + B \times (Age) + C \times (Age \times Age) + D$$

$$where\ A = 0.0212126,\ B = -0.0002587,\ C = -0.0000332,\ D = 0.9508566$$

The ratio between the utility for the general population at start age and that of the mean cohort age at each cycle was applied within the model.

Adverse events

Given that the main outcome measures being used from the clinical trials are VFQ-25 and EQ-5D, it is assumed that these will capture the quality of life impacts associated with adverse events during the period in which the treatment is provided.

Utility associated with blindness

There were two studies of utilities associated with blindness based in the UK,[104, 108] which the AG thought to be the best sources of evidence. Both studies have been used within previous NICE appraisals.[109-113] Czoski-Murray *et al.* used contact lenses to simulate blindness associated with macular degeneration,[104] whilst Brown *et al.*[108] estimated utility according to valuations by patients with a range of conditions associated with blindness. The AG used the time trade-off values reported in these studies. Each study provided utilities for different levels of blindness, and the AG calculated a weighted average based on the number of patients within the studies falling into each category. This assumes that patients with uveitis would have a similar distribution for the severity of blindness. The study by Czoski-Murray *et al.* was used in the base case analysis as it was based on public valuations of utility; however, it does not provide utilities for the worst states of blindness and may therefore overestimate the overall utility associated with blindness. This resulted in a utility associated with blindness of 0.38. Uncertainty around this parameter was modelled using the variance-covariance matrix provided within the study. The utility estimated from the study by Brown *et al.*[108] (0.57) was employed within sensitivity analysis.

Resource use and costs

Treatment costs

The cost of adalimumab, dexamethasone, immunosuppressants and corticosteroids were based on the latest drug tariff.114 Drug acquisition costs included within the model are presented in **Error! Reference source not found.**.

2) Incidence and HRQoL impact of blindness

Since there is limited evidence around the rate of legal blindness for this patient group, and there is no evidence around the impact of treatment upon this rate, the AG performed exploratory analyses around these parameters. This was done by varying the rate of legal blindness in patients with uveitis who are treated with (limited) current practice (from 0 to 0.0374) based upon alternative sources[16, 25] (See 'permanent blindness' section), and the relative risk of legal blindness cases avoided owing to the effect of treatments (from 0 to 1).

These analyses were also undertaken using (i) alternative utilities from Brown et al.[108] and (ii) a higher cost of blindness based upon the upper bound of the 95% confidence interval for this parameter.

3) Patients who go into remission due to adalimumab treatment

A proportion of patients who continue treatment with adalimumab may achieve remission. The base case analysis assumes that these patients would continue to receive adalimumab until treatment failure; however, the clinical advisors to the AG suggested that after around two years of stable disease, patients may no longer require treatment but because they are in remission they may maintain the same level of HRQoL as that whilst on treatment. This sensitivity analysis therefore assesses the impact of assuming that, after two years on treatment, a range of proportion of patients (0 – 1) would no longer receive adalimumab, but their HRQoL would only decrease due to age, until the treatment failure curve predicts failure or until they die due to other causes.

4) Using the VFQ-25 data from the VISUAL trials of adalimumab to map to EQ-5D utility data

This sensitivity analysis assesses the impact of using the regression analysis of the HURON trial data to map the VFQ-25 data from the VISUAL trials to EQ-5D utilities.

5) Extrapolation of time to treatment discontinuation for adalimumab

The impact of using alternative plausible parametric distributions (Weibull, Gompertz) for time to treatment discontinuation was explored.

6) Varying the time period over which the utility decreases to that of baseline after treatment

The treatment effect beyond six months for dexamethasone and beyond treatment discontinuation for adalimumab is unknown. Within the base case, patients receiving dexamethasone are assumed to take four weeks to return to baseline utility beyond the trial follow-up of six months. HRQoL for patients receiving adalimumab is assumed to return to baseline immediately upon treatment discontinuation.

Table 14: Univariate sensitivity analyses for DEX 700 + LCP(H) vs LCP(H). Base case ICER: £20,058 per QALY (deterministic)

Parameters	Base case, lower value, upper value	ICER based on lower value	ICER based on upper value
Utilities			
Baseline utility	0.79, 0.77, 0.80	£20,346	£19,783
Blindness utility	0.38, 0.31, 0.57	£18,551	£25,257
Administration and monitoring	0.35, 0.28, 0.42		
Monitoring visit frequency	6 weeks, 4 weeks, 8 weeks	£20,545	£19,814
Monitoring visit cost	£44, £35.80, £53.03	£19,854	£20,282
Dexamethasone implant administration cost	£113.42, £91.15, £135.65	£19,326	£20,863
AE costs			
Raised IOP	£23.42, £19.06, £28.23	£20,024	£20,095
Cataract surgery	£852.40, £658.33, £1019.47	£19,534	£20,635
Glaucoma procedure	£581.25, £467.32, £695.17	£20,173	£19,931
Hypertension	£7.04, £5.66, £8.42	£20,058	£20,057
Blindness (transition)	£237, £191, £283	£20,061	£20,054
Blindness (annual)	£7,659, £6,158, £9,160	£21,807	£18,308

The model results are generally robust to changes to the values of these parameters. The model is therefore most sensitive to assumptions around the comparator, assumptions around permanent blindness and the duration of the treatment effect.

6.2.2.1 Adalimumab – active uveitis patients

Base case

The base case results are presented in **Error! Reference source not found.**. In the base case, adalimumab in combination with limited current practice as provided in the VISUAL I trial (LCP(VI)) was estimated to produce 0.194 incremental QALYs compared with LCP(VI) alone in patients with active uveitis at an additional cost of £18,321, resulting in an ICER of £94,523 per QALY gained. The ICER generated using the deterministic version of the model (£95,506) was similar to that from the probabilistic model (see **Error! Reference source not found.**). A breakdown of the results of the deterministic analysis is provided in Appendix 8. **Error! Reference source not found.** and shows the CEAC of ADA + LCP(VI) versus LCP(VI) in patients with active uveitis. The AG notes that within the VISUAL I trial both treatment groups included an initial systemic steroid burst which was tapered by week 15 and that around 30% of patients on both arms received systemic immunosuppressants.[4, 5]

Potentially important subgroups

The model is made up of a heterogeneous population, and it may be that the interventions are more cost-effectiveness in some groups than others. However, there is insufficient evidence to undertake any formal subgroup analyses. This discussion considers the key subgroups for which the interventions may be more cost-effective. Almost all patients receiving adalimumab will have bilateral uveitis; however dexamethasone may also be given to patients with unilateral uveitis. Dexamethasone is likely to be more cost-effective when given in one eye to patients with bilateral uveitis because BCVA in the better-seeing eye is the best predictor of quality of life and hence bilateral uveitis patients are generally able to benefit more from treatment than unilateral uveitis patients, at the same cost of treatment. Where the annual rate of blindness is set to 0, the results could be used to give an indication around the cost-effectiveness of dexamethasone for patients with unilateral disease (since patients with unilateral disease are unlikely to become legally blind, unless their disease progresses to become bilateral). This results in an ICER of £48,937. It is important to note that the treatment effect may also be different (expected to be reduced) for unilateral patients compared with a pooled group of unilateral and bilateral patients; however there is no evidence available to model this.

Patients also have the potential to benefit more from treatment with adalimumab or dexamethasone if they have more severe uveitis, and hence the treatments are likely to be more cost-effective as the baseline disease worsens. In addition, patients with macular oedema would be more likely to go blind and hence the interventions of interest, in particular adalimumab due to the longer duration of treatment, are more likely to prevent cases of blindness and hence are likely to be more cost-effective in this group.

Model perspective

Currently, the base case analysis takes an NHS and PSS perspective. However, sight problems and sight damage caused by uveitis can affect every aspect of daily life. The quality of life measures used within the health economic model aim to largely capture these effects. However, if a societal perspective was taken, the cost-effectiveness of the interventions would be reduced. A societal perspective would capture the additional cost savings associated with increased leisure time and workplace productivity resulting from the benefits of the interventions. Given that non-infectious uveitis affects a working-age population these cost savings would not be negligible. Therefore, there are likely to be additional non NHS and PSS costs and benefits of the interventions not captured within our analyses; however these additional costs are beyond the scope of a NICE appraisal.

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Appendix 8: Breakdown of the cost-effectiveness analysis results for the base case

Table 15: Breakdown of the results of the base case analysis for dexamethasone versus limited clinical practice (deterministic)

	Sham	Dexamethasone	Incremental
LYs			
On treatment	18.669	18.703	0.034
Blind	1.859	1.826	-0.034
Total	20.529	20.529	0.000
QALYs			
On treatment	13.904	13.946	0.042
Blind	0.709	0.696	-0.013
Total	14.613	14.641	0.029
Costs			
Drug costs	£2,449.61	£3,324.03	£874.42
Admin. and monitoring	£17,452.41	£17,597.44	£145.04
AEs	£5,186.39	£5,255.04	£68.64
Rescue therapy	£285.26	£35.25	-£250.01
Blindness	£14,281.54	£14,023.09	-£258.46
Total	£39,655.21	£40,234.85	£579.64
ICER (£/QALY)			**£20,057.73**

Table 16: Breakdown of the results of the base case analysis for adalimumab versus limited clinical practice in patients with active uveitis (deterministic)

	Placebo	Adalimumab	Incremental
LYs			
On treatment	0.620	2.081	1.460
Failed treatment	17.565	16.323	-1.242
Remission	0.000	0.000	0.000
Blind	2.343	2.125	-0.218
Total	20.529	20.529	0.000
QALYs			
On treatment	0.524	1.799	1.274
Failed treatment	13.603	12.595	-1.008
Remission	0.000	0.000	0.000
Blind	0.792	0.716	-0.076
Total	14.919	15.110	0.191
Costs			
Drug costs	£2,813.59	£21,961.73	£19,148.14
Admin. & monitoring	£18,352.07	£18,811.80	£459.73
AEs	£8,037.18	£8,338.60	£301.43
Blindness	£17,983.53	£16,289.21	-£1,694.32
Total	£47,186.36	£65,401.34	£18,214.98
ICER (£/QALY)			**£ 95,505.74**

Table 17: Breakdown of the results of the base case analysis for adalimumab versus limited clinical practice in patients with inactive uveitis (deterministic)

	Placebo	Adalimumab	Incremental
LYs			
On treatment	2.937	4.223	1.286
Failed treatment	15.137	14.104	-1.034
Remission	0.000	0.000	0.000
Blind	2.454	2.202	-0.252
Total	20.529	20.529	0.000
QALYs			
On treatment	2.458	3.519	1.061
Failed treatment	11.957	11.100	-0.856
Remission	0.000	0.000	0.000
Blind	0.830	0.742	-0.088
Total	15.244	15.361	0.116
Costs			
Drug costs	£4,990.76	£43,855.57	£38,864.81
Admin. & monitoring	£19,944.05	£20,708.76	£764.71
AEs	£4,345.10	£4,002.68	-£342.42
Blindness	£18,830.87	£16,894.93	-£1,935.94
Total	£48,110.78	£85,461.94	£37,351.16
ICER (£/QALY)			**£321,405.45**

ADDENDUM

Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence

Title: Adalimumab and dexamethasone for treating non-infectious intermediate, posterior or pan uveitis in adults

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Hazel Squires, Senior Research Fellow, ScHARR Edith Poku, Research Fellow, ScHARR Inigo Bermejo, Research Associate, ScHARR Katy Cooper, Senior Research Fellow, ScHARR John Stevens, Reader in Decision Science, ScHARR Jean Hamilton, Research Associate, ScHARR Ruth Wong, Information Specialist, ScHARR Alastair Denniston, Consultant Ophthalmologist (Uveitis and Medical Retina), University Hospitals Birmingham NHS Foundation Trust, UK Ian Pearce, Director of Clinical Eye Research Centre, St Paul's Eye Unit, Royal Liverpool University Hospital, UK Fahd Quhill, University Senior Lecturer and Consultant Ophthalmologist (Specialist interest in Medical Retina), Sheffield Teaching Hospitals NHS Foundation Trust, UK
Correspondence Author	Hazel Squires, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, S1 4DA UK. Email: h.squires@sheffield.ac.uk

Date completed	Date completed (30/11/2016)

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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

Due to the uncertainties and substantial impact upon the model results of the exploratory analysis 2 and 3 for adalimumab in active patients, Tables A and B below show the results of an additional exploratory analysis combining varying the relative risk of blindness with treatment and the rate of treatment discontinuation following remission (whilst maintaining benefit), using the rate of blindness for the comparator from the study by Dick et al and Durrani et al respectively.

Table A: Exploratory analysis showing the ICERs of adalimumab versus LCC(VI) using the blindness rate reported by Dick et al. and assuming different RRs of blindness and remission rates

Rate of remission*	RR of blindness until treatment failure				
	0	**0.25**	**0.5**	**0.75**	**1**
0	£95,506	£110,263	£129,611	£156,077	£194,471
0.05	£77,414	£90,126	£106,777	£129,541	£162,547
0.1	£67,363	£78,848	£93,889	£114,448	£144,253
0.2	£56,214	£66,261	£79,419	£97,403	£123,473
1	£35,299	£42,476	£51,876	£64,726	£83,353

* Annual rate of patients going into remission and discontinuing treatment whilst maintaining the benefit, if remaining on treatment at 2 years

Table B: Exploratory analysis showing the ICERs of adalimumab versus LCP(VI) using the blindness rate reported by Durrani et al. and assuming different RRs of blindness and remission rates

Rate of remission*	RR of blindness until treatment failure				
	0	**0.25**	**0.5**	**0.75**	**1**
0	£33,003	£44,570	£63,587	£100,494	£202,592
0.05	£25,171	£35,800	£53,081	£86,392	£178,191
0.1	£20,821	£30,708	£46,738	£77,576	£162,462
0.2	£15,994	£24,866	£39,237	£66,867	£142,883
1	£6,942	£13,443	£23,995	£44,308	£100,230

*Annual rate of patients going into remission and discontinuing treatment whilst maintaining the benefit, if remaining on treatment at 2 years

Adalimumab

(HUMIRA®)

National Institute for Health and Care Excellence (NICE)

Health Technology Appraisal

Uveitis (non-infectious) - adalimumab and dexamethasone [ID763]

19th August 2016

Submission by AbbVie

Appraisal technology: Adalimumab (HUMIRA®)

Submission prepared by:

AbbVie,
AbbVie House,
Vanwall Business Park,
Vanwall Rd,
Maidenhead,
Berkshire
SL6 4UB

Date of submission: 19th August 2016

Company contacts:

Andrew Miniuks
Head of HTA
AbbVie,
AbbVie House,
Vanwall Business Park,
Vanwall Rd,
Maidenhead,
Berkshire
SL6 4UB

Tel: 01628 561 090
Fax: 01628 644185
E-mail: andrew.miniuks@abbvie.com

Peter Dale,
Senior HE Manager,
AbbVie,
AbbVie House,
Vanwall Business Park,
Vanwall Rd,
Maidenhead,
Berkshire
SL6 4UB

Tel: 07500 920842
Fax: 01628 644185
E-mail: pdale@abbvie.com

DECLARATION

This submission does not omit any relevant evidence of which AbbVie is aware of and is not currently in the public domain, which could reasonably be considered to be related to the appraisal of adalimumab (HUMIRA®) for the treatment of non-infectious, intermediate, posterior or pan uveitis.

Information within this dossier considered as academic in confidence is underlined and highlighted in yellow and information considered commercial-in-confidence is underlined and highlighted in blue.

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Abbreviations

AC	Anterior chamber
ACR	American College of Rheumatology
ADA	Adalimumab
AE	Adverse events
ARVO	Association for Research in Vision and Ophthalmology
AS	Ankylosing spondylitis
AZA	Azathioprine
BSC	Best supportive care
CMO	Cystoid macular oedema
CRT	Central retinal thickness
CSR	Clinical study report
DMARD	Disease modifying anti-rheumatic drugs
E/100PYs	Events per 100 patient years
EOW	Every other week
EQ-5D	EuroQol five dimensions questionnaire
ETDRS	Early Treatment of Diabetic Retinopathy Study
EULAR	European League Against Rheumatology
EVER	European Association for Vision and Eye Research
HADS	Hospital Anxiety and Depression Scale
HLA	Human leukocyte antigen
HRQOL	Health related quality of life
HR	Hazard ratio
HRU	Healthcare resource use
HS	Hidradenitis suppurativa
IOP	Intraocular pressure
IRR	Incidence rate ratio
ITT	Intention to treat
IVRS/IWRS	Interactive Web and Voice Response System

JIA	Juvenile idiopathic arthritis
LOCF	Last observation carried forward
logMAR	Logarithm of the Minimal Angle of Resolution
OCT	Ocular coherence tomography
PBO	Placebo
PRO	Patient reported outcomes
SAE	Serious adverse events
SC	Subcutaneous
SF-6D	Short Form–6 dimensions
SUN	Standardization of Uveitis Nomenclature
TNF	Tumour necrosis factor
VFQ	Visual functioning questionnaire
VH	Vitreous haze
VRQOL	Vision-related quality of life
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire (specific health problem)

1 Executive summary

1.1 Background and context

Uveitis is caused by inflammation of the uveal tract of the eye and typically presents as painful, photophobic, red eye(s) and blurred vision[1]. It can potentially result in loss of vision, indeed, uveitis accounts for approximately 10% of cases of blindness in people of working age in the Western world[2].

Uveitis is defined by its anatomical location, onset, duration, cause and course[1]. The focus of this submission is patients with non-infectious, intermediate, posterior and pan uveitis[3].

Most cases of uveitis occur in people of working age which has considerable implications for both the individual and for society[4,5].

Patients with non-infectious intermediate, posterior and pan uveitis are more likely to suffer vision loss than those with anterior disease and to become blind earlier in the course of the disease[6]. These patients have markedly poorer health related quality of life (HRQOL) compared with the general population; visual impairment is a key factor in influencing HRQOL[7-10].

Healthcare and indirect (work loss/leaving the workforce) resource use and costs are significantly increased in patients with non-infectious intermediate, posterior and pan uveitis compared with the general population[11,12]. Patients with vision loss have even higher healthcare costs[13].

Non-infectious intermediate, posterior and pan uveitis account for around one-quarter of all uveitis cases[3]. Estimates suggest that there are around 5,000 people with a diagnosis of non-infectious intermediate, posterior and pan uveitis in England[14].

The aim of treatment for all types of uveitis is to reduce inflammation, improve vision and prevent further deterioration of vision loss.

Corticosteroids are the first-line treatment for chronic non-infectious uveitis[3]. Corticosteroids should be used with care because of the associated complications, related to the dose and duration of treatment, which include ocular complications (e.g. raised intraocular pressure [IOP] and formation of cataract) and systemic complications such as osteoporosis, diabetes, susceptibility to infection, adrenal suppression and changes in mood and behaviour[1,15]. Ocular damage increases with length of exposure to corticosteroids and delivery via injection or implant appears to carry a higher risk of damage than oral delivery[16].

Systemic immunosuppression is initiated second-line for patients in whom ocular inflammation has recurred on reducing the steroid dose or who have poorly controlled ocular inflammation with systemic steroids[1]. Immunosuppressive treatment is begun early in the treatment of certain diseases—for example, posterior disease or pan uveitis associated with Behçet's syndrome, in which visual outcomes have been shown to be poor with corticosteroids alone[15]. Many patients taking systemic drugs require a combination of two or more immunosuppressive agents, with or without corticosteroids, to control their ocular inflammation. Most commonly used immunosuppressive agents, such as methotrexate, are unlicensed for uveitis.

Biologic agents, such as adalimumab (ADA) are used as the final line of therapy in patients who have not responded to or are unable to tolerate steroids and/or immunosuppressants[1].

1.2 Adalimumab (Humira®)

ADA is licensed for the treatment of non-infectious intermediate, posterior and pan uveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate[17].

ADA, a cytokine modulator or TNF-inhibitor, reduces inflammation by inhibiting the activity of the pro-inflammatory cytokine tumour necrosis factor alpha (TNF-α). ADA has been recommended as a

treatment by NICE for a number of inflammatory conditions including: rheumatoid arthritis, juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), psoriatic arthritis, plaque psoriasis, hidradenitis suppurativa, Crohn's disease and ulcerative colitis[18]. NHS England have commissioned ADA for children and adolescents with severe refractory anterior uveitis[19].

1.3 Clinical evidence for efficacy

The phase III clinical trial programme for ADA in non-infectious intermediate, posterior and pan uveitis consists of two randomised controlled trials versus placebo (PBO) (VISUAL I and VISUAL II) and an open label extension study including patients from both trials (VISUAL III). VISUAL I and II were similar in study design, however, VISUAL I included patients with active uveitis, whereas VISUAL II included patients with controlled disease.

ADA demonstrated a positive effect versus PBO in both populations: patients with active disease despite corticosteroid use for at least 2 weeks (oral prednisone ≥10 mg/day to ≤60 mg/day or oral corticosteroid equivalent) and those with controlled disease requiring corticosteroid use to maintain inflammation control (oral prednisone ≥10 mg/day to ≤35 mg/day or oral corticosteroid equivalent)[20-22].

The composite primary end-point of time to treatment failure, a composite measure of inflammation and visual acuity (retinal vascular lesions, anterior chamber [AC] cell grade*, vitreous haze [VH] grade† and visual acuity) was significantly extended by the use of ADA[20,21].

- In VISUAL I, the median time to treatment failure was 24 weeks (5.6 months) in the ADA group and 13 weeks (3 months) in the PBO group, representing a significant 50% reduction in the risk of treatment failure in those patients receiving ADA (HR was 0.5 [95% CI: 0.36–0.70]), p<0.001[21].

- In VISUAL II, the median time to treatment failure was not reached in the ADA group (>18 months) and was 8.3 months in the PBO group, representing a significant 43% reduction in the risk of treatment failure in those patients receiving ADA (HR was 0.57 [95% CI: 0.39–0.84]), p=0.004[22].

The secondary end-points demonstrated significant benefit in visual acuity, inflammation, macular oedema and vision related QOL (VRQOL) with ADA compared with PBO in VISUAL I. In VISUAL II, although benefit was seen numerically with ADA for most measures, the benefit did not reach significance. This might be due to the differences in disease activity at baseline between the two studies – controlled disease rather than active disease[21,22].

In both studies, ADA showed early and sustained activity: the Kaplan-Meier curves separated early – at the first measurable time-point (week 6 in VISUAL I and week 2 in VISUAL II). Benefit in the ADA arm was sustained for 5.6 months in VISUAL I and for >18 months in VISUAL II without the use of steroids[21,22].

Visual acuity was maintained for significantly longer with ADA compared with PBO in both VISUAL studies. The risk of treatment failure based on visual acuity alone was reduced in patients receiving ADA by 44% in VISUAL I and by 67% in VISUAL II compared with PBO. Macular oedema is a major cause of vision loss in people with uveitis[1]. The significant benefit seen with ADA over PBO in a pre-specified *post hoc* analysis in patients without macular hole and/or retinal detachment in VISUAL I suggests that ADA slows the development of macular oedema in patients with active disease[21].

Prolonged steroid use is not recommended and corticosteroids need to be used with care because of the associated complications, related to the dose and duration of treatment[1]. In both VISUAL studies, patients were able to stop using corticosteroids until treatment failure. The proportions of patients in quiescence and steroid-free quiescence were significantly higher in the ADA group compared to PBO in both studies[20,21].

* AC cell grade is a measure of inflammation in the AC, an increase in the number of AC cells may reduce visual function.
† Measures inflammation in the vitreous, a higher VH grade may lead to increasingly blurred vision.

Loss of sight has a significant impact on patients' QOL and ability to work. Significant benefits were seen in VRQOL (total score, general vision, ocular pain, near vision and mental health) (as measured by VFQ-25), in HRQOL (as measured by EQ-5D) and in ability to work in patients receiving ADA compared to those receiving PBO in VISUAL I. There were no differences in patient reported outcomes (PRO) for VISUAL II[20-22].

The clinical benefits with ADA observed in the VISUAL I and II studies were continued during the extension study (VISUAL III)[23].

1.4 Clinical evidence for safety

Adverse events (AEs) were broadly similar between the ADA and PBO groups in both VISUAL studies and discontinuation rates were low. The most frequently reported AEs in VISUAL I and VISUAL II were nasopharyngitis, fatigue and headache. Most events occurred in <10% of patients and rates were comparable between ADA and PBO[20-22]. The safety profile was consistent with the known safety profile of ADA across all approved indications and no new safety signals were identified in either study[20-22,24].

There was one death in VISUAL I and one in VISUAL II, both were in patients receiving ADA, however, the deaths were not considered to be related to ADA treatment[20,21].

Long-term safety AE rates were comparable to those seen in the VISUAL I and VISUAL II trials. In VISUAL III, rates were 577 AE/100 patient years and 19.6 serious AE/100 patient years[23].

1.5 Implications for the NHS

For the purpose of the budget impact calculation we have only included drug acquisition costs to the NHS. The annual cost per patient of treating non-infectious intermediate, posterior and pan uveitis with ADA is estimated to be £9,507.78 in Year 1 and £9,155.64 in subsequent years.

The total number of patients expected to be treated with ADA is 175 in Year 1 rising to 556 in Year 5. The total budget impact of ADA introduction is expected to be £1,551,011 in Year 1 rising to £4,766,996 by Year 5.

2 Background and context

2.1 Introduction to uveitis

- Uveitis is a potentially blinding condition caused by inflammation of the uveal tract of the eye[1]. Uveitis accounts for approximately 10% of cases of blindness in people of working age in the Western world[2].
- Uveitis is defined by its anatomical location, onset, duration, cause and course[1]. This submission is concerned with non-infectious, intermediate, posterior and pan uveitis.
- Intermediate, posterior and pan uveitis are less common than anterior uveitis but are more severe and more likely to cause vision loss[3].
- Most non-infectious, intermediate, posterior and pan uveitis is idiopathic, however, systemic autoimmune disorders play a role in around one-third of cases[25].
- Uveitis typically presents with a painful, photophobic, red eye and blurred vision, although patients may not have all these symptoms at the start of an attack[1]. The clinical features of uveitis vary depending on the location of the inflammation and tend to be more severe in patients with intermediate, posterior and pan uveitis than in patients with anterior disease.
- The complications of uveitis can be sight-threatening and may require surgical intervention – the major causes of vision loss in people with uveitis are cystoid macular oedema (CMO), secondary cataract and secondary glaucoma[26].
- Most cases of uveitis occur in people of working age[4,5].
- Patients with non-infectious intermediate, posterior and pan uveitis are more likely to suffer vision loss than those with anterior disease and to become blind earlier in the course of the disease[6].
- Patients with non-infectious intermediate, posterior and pan uveitis have markedly poorer health related quality of life (HRQOL) compared with the general population; visual impairment is a key factor in influencing HRQOL[7-10].
- Healthcare and indirect (work loss) resource use and costs are significantly increased in patients with non-infectious intermediate, posterior and pan uveitis compared with the general population[11].
- Patients with non-infectious intermediate, posterior and pan uveitis and with ocular complications have significantly greater healthcare costs than patients with non-infectious intermediate, posterior and pan uveitis and no ocular complications, patients with pan uveitis incur the greatest healthcare burden[13].
- The risk of leaving the workforce is significantly increased in patients with non-infectious, intermediate, posterior and pan uveitis compared with the general population, driven by increases in absence and long-term disability[12].
- Non-infectious intermediate, posterior and pan uveitis account for around one-quarter of all uveitis cases[3]. Estimates suggest that there are around 5,000 people with a diagnosis of non-infectious intermediate, posterior and pan uveitis in England[14].

Uveitis, inflammation of the uveal tract of the eye, is a major cause of blindness and visual impairment[1]. Uveitis accounts for approximately 10% of cases of blindness in people of working age in the Western world[2].

A retrospective review of patients attending a uveitis clinic in the UK between 1998 and 2000 found that 70% of patients had visual impairment (visual acuity 6/18 or worse) and over half (58%) of patients with visual impairment had severe visual loss (≤6/60)[27]. The major causes of visual loss in people with uveitis were CMO, secondary cataract and secondary glaucoma[26], which may require surgical intervention.

The uveal tract is made up of the iris, ciliary body (or ciliary muscle) and the choroid[28]. The inflammatory processes associated with uveitis may also affect nearby tissues including the retina, optic nerve and vitreous body[26].

Uveitis can be defined by its anatomical location, onset, duration, cause and course. The classification of uveitis based on consensus from the Standardization of Uveitis Nomenclature (SUN) Working Group is outlined below[3,29].

Anatomical location (please see Figure 1 overleaf for a diagram of eye anatomy).

- Anterior—primary site of inflammation is the anterior chamber (AC), this includes iritis (inflammation that is confined to the AC) and iridocyclitis (inflammation that is confined to the AC and anterior vitreous).

- Intermediate—primary site of inflammation is the vitreous, although the ciliary body and pars plana may also be affected.

- Posterior—primary site of inflammation is the retina or choroid. Inflammation of any combination of the following: the choroid (choroiditis), retina (retinitis) or optic nerve head (papillitis).

- Pan uveitis—inflammation in AC and vitreous and retina or choroid.

By definition intermediate, posterior and pan uveitis is often referred to uveitis affecting the posterior segment of the eye whereas anterior uveitis only affects the anterior segment of the eye.

Onset

- Sudden or insidious.

Duration

- Limited (≤3 months) or persistent (>3 months).

Course

- Acute—sudden onset and limited duration.

- Recurrent—repeated episodes separated by periods of inactivity without treatment of ≥3 months' duration.

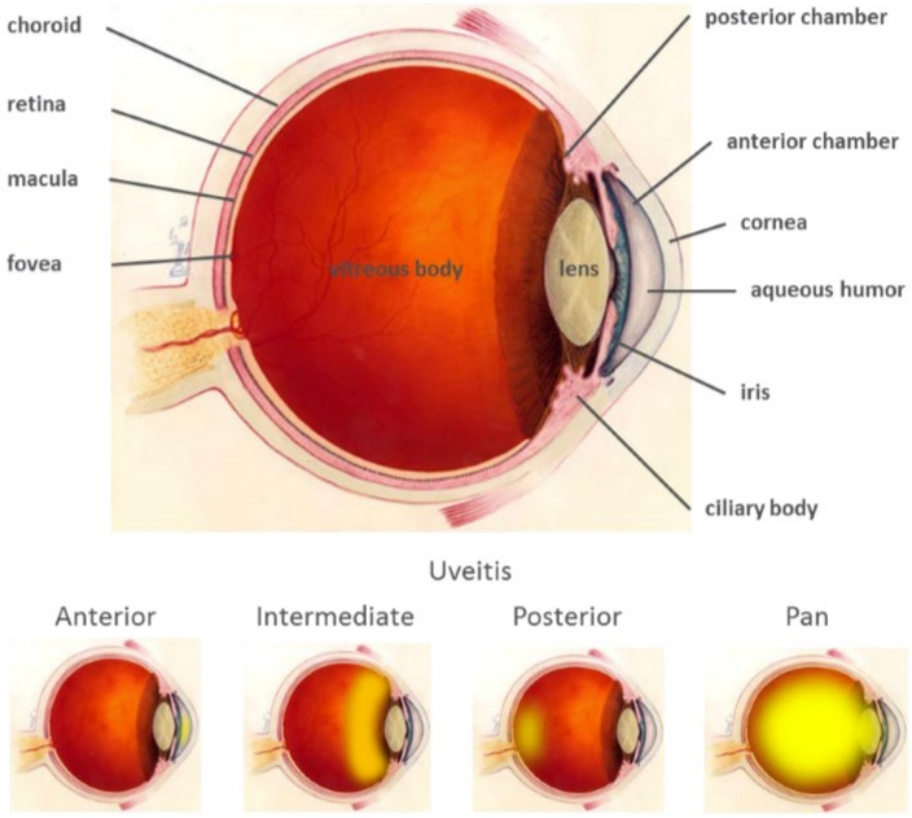
- Chronic—persistent uveitis with relapse in <3 months after discontinuing treatment.

Uveitis may be further sub-divided by cause: infectious or non-infectious and by the number of eyes involved (bilateral or unilateral).

This submission is concerned with non-infectious intermediate, posterior and pan uveitis and as such the focus of the submission will be this patient subgroup. In general intermediate, posterior and pan uveitis are less common than anterior uveitis but are more severe and more likely to cause vision loss[3].

Figure 1 (overleaf) illustrates the anatomy of the eye and the anatomical classification of uveitis.

Figure 1: Anatomy of the eye and the anatomical classification of uveitis.



2.1.1 Causes and risk factors

Most uveitis is idiopathic; however, when a cause is identified, it usually includes one of the following: systemic autoimmune disorders, infection, trauma or neoplasia[26]. As discussed earlier the focus of this submission is non-infectious intermediate, posterior and pan uveitis.

A number of systemic autoimmune disorders may lead to non-infectious intermediate, posterior and pan uveitis, including:

- Behçet's disease.
- Sarcoidosis.
- Psoriasis (with or without associated arthritis).
- Seronegative spondyloarthropathies (ankylosing spondylitis [AS], juvenile rheumatoid arthritis, Reiter's syndrome and inflammatory bowel disease).
- Multiple sclerosis.

A large cross-sectional study of 580 patients, with all types of non-infectious uveitis in the US, reported pre-existing conditions according to anatomical subtype[25]. Overall, 62% of people with non-infectious intermediate, posterior and pan uveitis had no known cause (idiopathic) for their disease and 36% had a systemic autoimmune disorder, the most common of which was sarcoidosis. See Table 1 for a breakdown by anatomical subtype.

Table 1: Pre-existing conditions in patients with non-infectious uveitis[25].

Pre-existing conditions	Total (n=580)	Anterior (n=168)	Intermediate (n=140)	Posterior (n=150)	Pan uveitis (n=122)
Idiopathic	58%	49%	84%	58%	42%
Systemic autoimmune disorders	40%	49%	16%	41%	54%
Sarcoidosis	32%	23%	23%	30%	30%
Ankylosing spondylitis	9%	15%	15%	14%	-
Crohn's disease	6%	13%	13%	9%	-
Rheumatoid arthritis	9%	13%	13%	9%	5%
Systemic lupus erythematosus	4%	1%	1%	-	14%
Vogt–Koyanagi–Harada syndrome	5%	1%	1%	-	9%
Eye trauma	2%	2%	-	1%	4%

People with a history of uveitis are more likely to have another episode of uveitis than people without a personal history. The presence of the genetic marker HLA (Human Leukocyte Antigen) also confers increased risk[30].

2.1.2 Symptoms and complications

The clinical features of non-infectious uveitis vary depending on the location of the inflammation[26]. They include the following:

- Pain in one or both eyes (pain may be worse when the person is contracting the ciliary muscle reading and otherwise contracting the ciliary muscle).
- Red eye (this is not always present).
- Diminished or blurred vision (although vision may be normal but become impaired later).
- Watering of the eye.
- Photophobia.
- Flashes and floaters.
- An unreactive or irregular-shaped pupil resulting from previous attacks.

Uveitis typically presents with a painful, photophobic, red eye and blurred vision, although patients may not have all these symptoms at the start of an attack. Posterior uveitis, particularly, may be bilateral and in such cases patients may present with white eyes and painless loss of vision. Floaters may be present if there is inflammation in the vitreous. Some types of uveitis, such as uveitis associated with juvenile idiopathic arthritis (JIA), are more insidious and such patients are often asymptomatic[1].

The large cross-sectional study of 580 patients with non-infectious uveitis mentioned above also looked at presenting symptoms according to anatomical subtype[25]. All patients experienced loss of vision; however, patients with posterior disease were more likely to have vision loss compared with patients with disease at other anatomical locations. Floating spots in the visual field and blurred vision were more frequent in patients with intermediate, posterior and pan uveitis and light sensitivity and ocular pain were more frequent in anterior uveitis.

Table 2: Symptoms at presentation in patients with non-infectious uveitis[25].

Ocular symptoms	Anterior (n=168)	Intermediate (n=140)	Posterior (n=150)	Pan uveitis (n=122)
Decreased vision	42%	48%	70%	55%
Floating spots/dark spots	9%	60%	57%	48%
Light sensitivity	70%	35%	35%	48%
Ocular pain	74%	28%	30%	57%
Redness	49%	18%	16%	48%
Blurred vision	37%	49%	69%	53%

The complications of uveitis can be sight-threatening – overall (non-infectious and infectious) uveitis is estimated to be responsible for about 10% of blindness in the Western world[2,26]. A retrospective review of patients attending a uveitis clinic in the UK found that 70% of patients had visual impairment (visual acuity 6/18 or worse) and over half (58%) of patients with visual impairment had severe visual loss (≤6/60)[27].

An analysis of a US database of 41,011 patients with uveitis (MedStat MarketScan database 2002-2008) revealed that patients with non-infectious intermediate, posterior and pan uveitis were more likely to become blind compared with patients with anterior disease (4.3% after three or more visits versus 1.5%). Furthermore, patients with non-infectious intermediate, posterior and pan uveitis became blind more quickly than those with anterior disease (mean time to blindness was 15.9 versus 11.6 months). Interestingly, only 3.2% of individuals who had anterior uveitis at the beginning of the study period received a subsequent diagnosis of posterior or pan uveitis[6].

The major causes of vision loss in people with uveitis are CMO, secondary cataract and secondary glaucoma. Glaucoma results from an increase in intraocular pressure (IOP), if left untreated elevated IOP can lead to damage to the optic nerve resulting in vision loss.

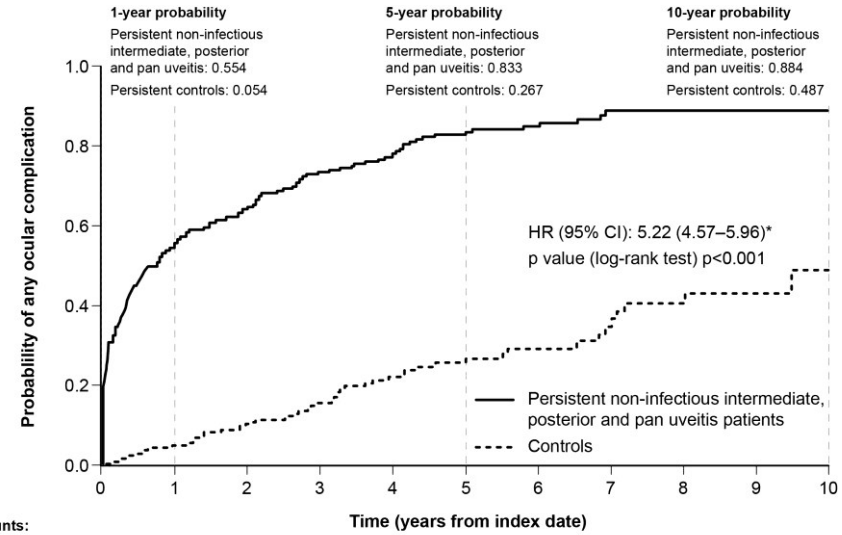
Data retrieved from a computerised database is available on 3,000 patients presenting to the Manchester Uveitis Clinic between 1991 and 2013[4]. These data include patients with both infectious and non-infectious disease. These data revealed that cataract was the most common complication occurring in around one-third of patients (34.9%). CMO was the next most common complication occurring in 20.5% of patients, macular oedema was most commonly seen in patients with intermediate disease (38.5% of all patients with intermediate disease had CMO). Glaucoma and ocular hypertension was the third most common complication occurring in 19.5% of patients. A number of other less common complications made up the remainder.

A study funded by AbbVie was presented at the European Association for Vision and Eye Research (EVER) in 2014[31]. The retrospective study assessed the risk of developing ocular complications in privately insured US patients with persistent non-infectious intermediate, posterior and pan uveitis (n=2,781) compared with matched healthy controls (n=2,769). Overall, there were 549 cases during the study period who were matched with controls, 302 of the cases had no ocular complications at baseline and were included in the study. Patients with persistent non-infectious intermediate, posterior and pan uveitis were nine-times more likely to develop ocular complications than controls, Table 3 details the risk of developing complications as calculated in an adjusted Cox regression analysis and illustrates the significant risk of visual disturbance, cataracts and glaucoma in patients with persistent non-infectious intermediate, posterior and pan uveitis. Figure 2 illustrates the time to onset of any ocular complication.

Table 3: Risk of developing ocular complications in patients with persistent non-infectious intermediate, posterior and pan uveitis[31].

	Hazard ratio (HR)	95% CI	p value
Any ocular complication	8.9	7.1–11.0	p<0.001
Visual disturbance	8.1	5.9–11.2	p<0.001
Cataracts	6.2	4.8–8.0	p<0.001
Glaucoma	4.2	3.0–5.9	p<0.001

Figure 2: Kaplan-Meier curve of time to onset of any ocular complication in patients with persistent non-infectious intermediate, posterior and pan uveitis[31].



Patient counts:

Non-infectious intermediate, posterior and pan uveitis	302	123	87	56	40	26	19	12	9	3	2
Controls	302	232	176	127	92	73	47	35	24	13	8

*HR and 95% CIs were estimated from adjusted Cox regression analyses

A similar study funded by AbbVie[32] assessed the risk of developing ocular complications in insured US patients with persistent non-infectious intermediate, posterior and pan uveitis compared with matched healthy controls (n=1,769). Patients with persistent non-infectious intermediate, posterior and pan uveitis were over 5-times more likely to have an ocular as compared to patients without non-infectious uveitis; 57.8% of the uveitis population ocular disorder compared with 16.7% of matched controls. Figure 3 illustrates the risk of developing ocular complications and

Figure 4 the time to onset of any ocular complication.

Figure 3: Risk of developing ocular complications in patients with persistent non-infectious intermediate, posterior and pan uveitis[32].

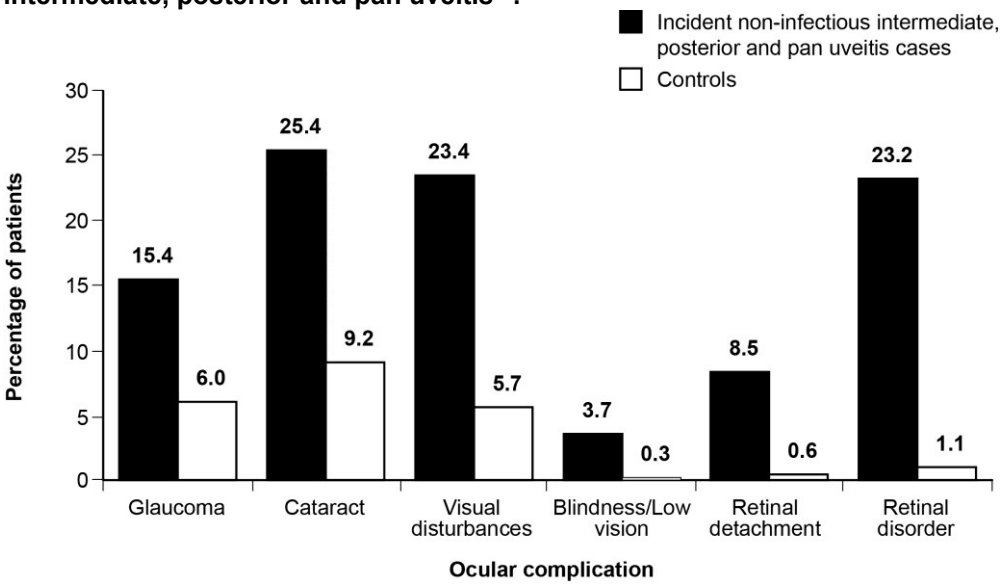
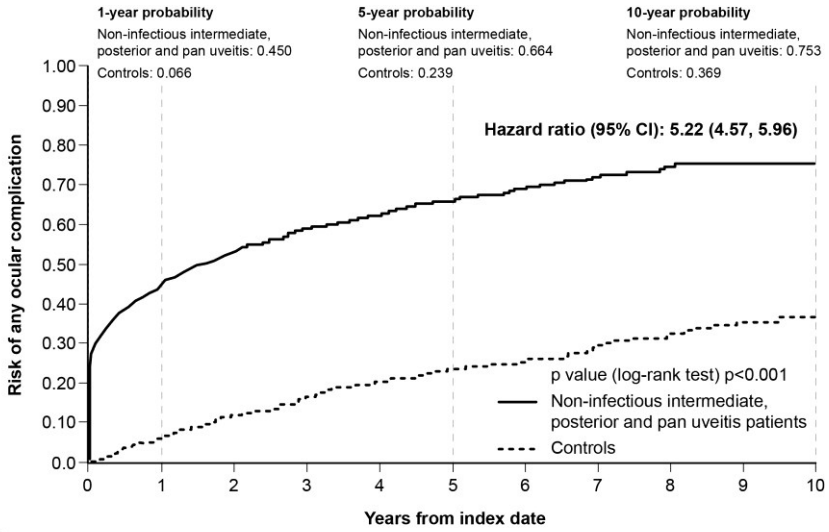


Figure 4: Kaplan-Meier curve of time to onset of any ocular complication in patients with persistent non-infectious intermediate, posterior and pan uveitis[32].



Patient counts:

Non-infectious intermediate, posterior and pan uveitis	783	524	361	267	194	138	88	54	24	18
Controls	1,284	926	680	492	367	263	189	127	78	46

2.1.3 Impact of disease

Uveitis and the complications of uveitis impact on many aspects of patients' lives, on their daily activities and on social and work lives. It has a significant impact on HRQOL and on mental health.

A number of studies have reported results demonstrating that patients with non-infectious, intermediate, posterior and pan uveitis have poorer HRQOL compared with the general population and that visual impairment is a key factor in influencing HRQOL[7-10].

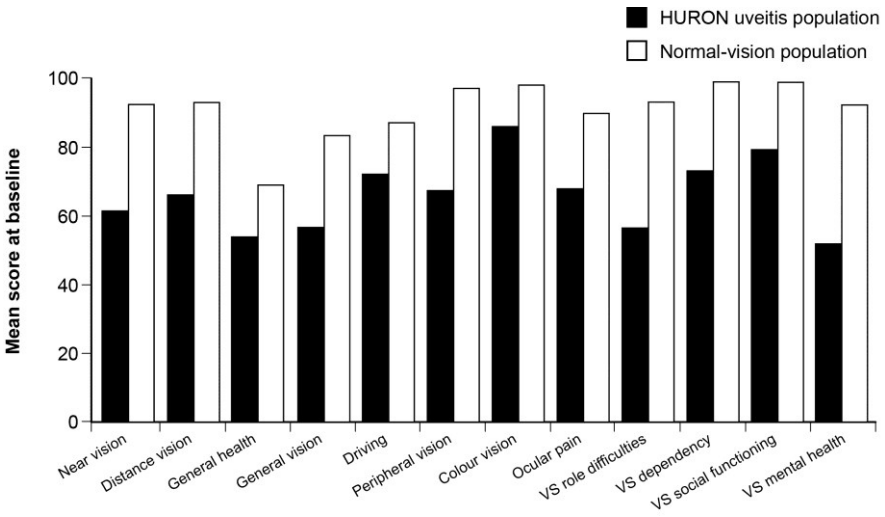
A prospective study conducted in specialist uveitis centres in the UK in 2002 investigated the impact of intermediate uveitis on visual performance and self-reported vision-related quality of life (VRQOL) and HRQOL using the VCM1 (a 10 item questionnaire that provides a subjective measure of concern regarding vision with scores ranging from 0.0 [best score] to 5.0 [worst score] with 50 intervals) and SF-36 respectively[8]. All 42 participants were diagnosed with intermediate uveitis and 67% had associated systemic disease. The VCM1 score was 0.8 (0.5–1.4) and 9.5% of all patients had a VCM1 score of over 2.0 (representing significantly impaired vision). Of the SF-36 subscales, social functioning, general health perception and pain were significantly ($p<0.01$) worse for patients with intermediate uveitis compared with the general population when matched for age and gender. Patients with significantly impaired vision (>2.0 on VCM1) had significantly lower physical and mental component scores, suggesting vision is a key factor influencing QOL in patients with intermediate uveitis.

A US-based study carried out a *post hoc* analysis of HRQOL and patient reported outcomes (PRO) in patients with non-infectious intermediate or posterior uveitis participating in a phase III clinical trial (the HURON trial) which assessed the safety and efficacy of dexamethasone intravitreal implant compared with sham treatment in patients with non-infectious intermediate or posterior uveitis[9]. Patients with intermediate or posterior uveitis had clinically and statistically significant impairment across all National Eye Institute Visual Function Questionnaire–25 subscales compared with a normal vision population. The subscales included vision-related domains, together with general health, driving, ocular pain and vision specific domains (mental health, dependency, social functioning and role difficulties), see Figure 5.

QOL was significantly impaired in the uveitis group when measured using the 36-Item Short-Form (SF-36) Health Survey mental component and the SF-6D dimensions when compared with the US general population ($p<0.001$).

This study demonstrates that visual impairment is a key factor influencing HRQOL and PRO and that poorer visual acuity correlates with reduced HRQOL and PRO across all measures.

Figure 5: Comparison of mean National Eye Institute Visual Function Questionnaire–25 scores between the uveitis population (n=224) and a normal-vision population (n=122)[9].
All p<0.001. VS indicates vision-specific.



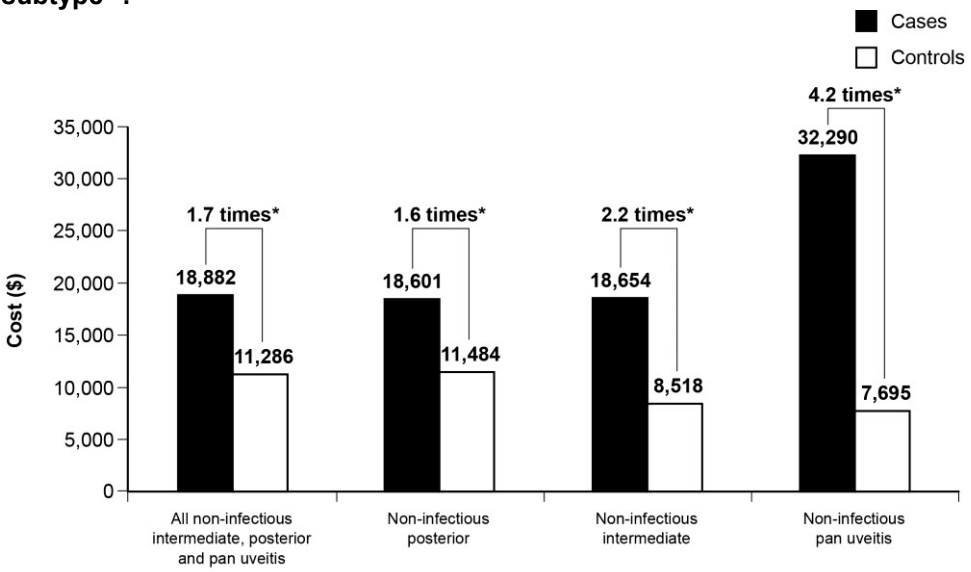
Uveitis also impacts on healthcare resources and on society. The cost of uveitis may be broken down into direct costs and indirect costs. Direct costs are those associated with healthcare resource use, e.g. hospitalisation, surgery, treatments and can be associated with the treatment of uveitis plus any complications. Indirect costs are costs to society or the patient and their family, e.g. lost productivity of patient and carer, informal care costs – these are likely to be increased in patients who become blind as a result of uveitis. Indeed, almost all of the costs of blindness are costs to society, a recent analysis of the cost of blindness in the Republic of Ireland found that only 1.96% of costs were due to direct healthcare costs[33].

Three similar case control studies, all of which were funded by AbbVie, used data from large US health claims databases to compare outcomes in patients with non-infectious, intermediate, posterior and pan uveitis with matched controls. All three studies have been presented at international meetings.

Direct (medical service and prescription drugs) and indirect (work loss) resource use and costs in privately insured US employees with non-infectious, intermediate, posterior and pan uveitis were compared to matched controls without uveitis from a large health claims database (705 cases and 705 matched controls)[11]. Patients with non-infectious, intermediate, posterior and pan uveitis used significantly more direct health care resources, in terms of more hospital visits compared with controls, accident and emergency (0.4 visits versus 0.2 visits) and outpatient visits (16.5 versus 7.6) and more prescription drugs (7.8 versus 4.1), p<0.05 for all. Work loss was also greater in the patients with non-infectious, intermediate, posterior and pan uveitis, in terms of mean disability days (10.3 versus 4.6), medically related absenteeism days (8.5 versus 3.8) and total work loss days (18.7 versus 8.4). After adjustment for baseline characteristics, total costs were higher for patients with non-infectious intermediate, posterior and pan uveitis; direct costs were more than twice as high ($11,424 versus $5,090) and indirect costs were doubled ($3,034 versus $1,510), p<0.05 for both.

The cost associated with ocular complications in non-infectious, intermediate, posterior and pan uveitis was compared using matched cases (with non-infectious, intermediate, posterior and pan uveitis and ocular complications) and controls (non-infectious, intermediate, posterior and pan uveitis, no ocular complications) from a large US health insurance database[13]. Cases and controls (n=1,327 in both arms) were followed up for 1 year post-complication. Total annual costs (medical and drug) were significantly higher in the patients with ocular complications: $18,882 versus $11,286. Patients with pan uveitis had the greatest cost difference ($32,290 versus $7,695), indicating the complication burden of this subtype, see Figure 6. Costs were driven by medical costs rather than drug costs.

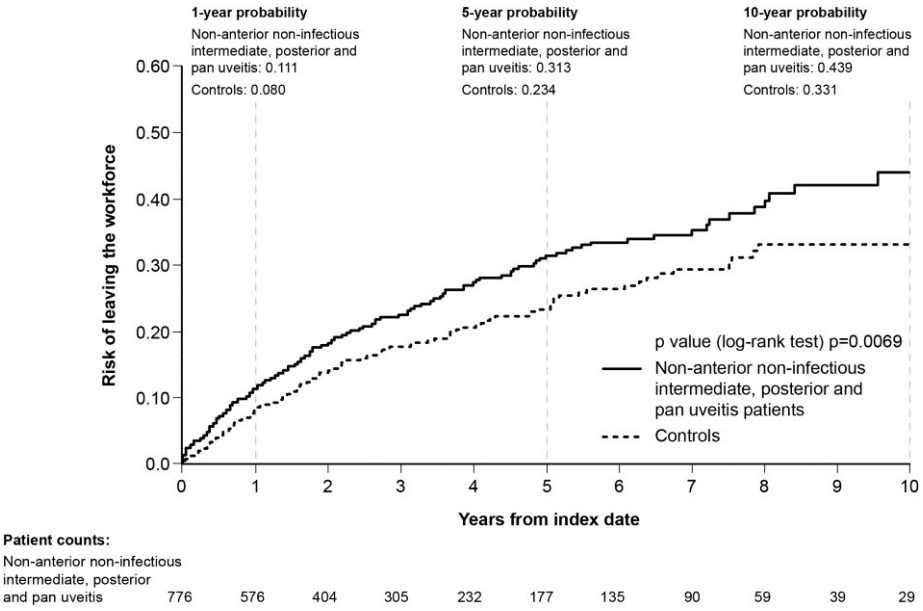
Figure 6: Total average costs 1 year post-complication by non-infectious non-anterior subtype[13].



*p<0.05 for non-infectious intermediate, posterior and pan uveitis versus controls

The risk of leaving the workforce (leave of absence, early retirement, short-term disability or long-term disability) in adults of working age (18-64 years, mean age 44.7 years) was compared in privately insured US employees with non-infectious, intermediate, posterior and pan uveitis and matched controls without uveitis from a large health claims database (776 cases and 776 matched controls)[12]. Risk of leaving the workforce was significantly higher in the group with non-infectious, intermediate, posterior and pan uveitis, p=0.0069, see Figure 7. At 5 years 31.3% of cases and 23.4% of controls had left the workforce and at 10 years 43.9% and 33.1% had left respectively. The risk of leaving the workforce was driven by leave of absence and long-term disability.

Figure 7: Risk of leaving the workforce early (any cause) in patients with non-infectious uveitis versus matched controls[12].



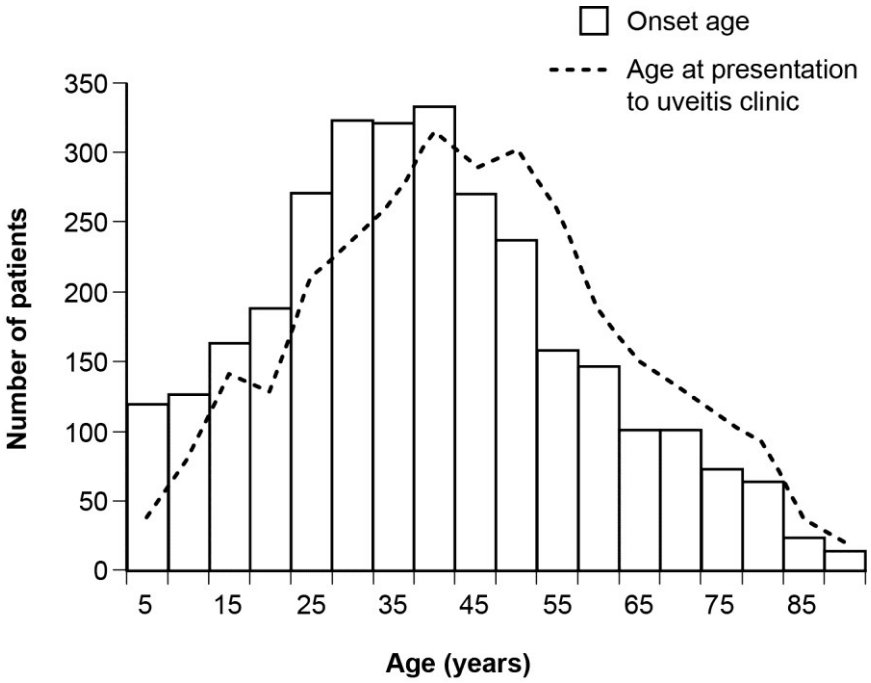
2.1.4 Epidemiology

Data from 3,000 patients attending the Manchester Uveitis Clinic provides contemporary epidemiological data for the UK[4,5].

In the Manchester cohort (infectious and non-infectious disease), most patients had anterior disease (46%), 11% had intermediate disease, 22% posterior disease and 21% had pan uveitis.

The age at presentation is shown in Figure 8 – the onset was in people of working age in the majority of cases (77.8%), although 13.4% of cases were in children aged under 16 years and 8.8% of cases were in older people aged over 65 years.

Figure 8: Age at onset and age at presentation for patients attending the Manchester Uveitis Clinic between 1991 and 2013[4].



Uveitis is slightly more common in women than in men (54% women and 46% men in the Manchester cohort). The gender ratio differed by form of uveitis, but the difference was only statistically significant in patients with chronic anterior uveitis (62% to 38%).

Uveitis was bilateral at presentation or became bilateral in 1,550 patients (51.7%). Of those with unilateral uveitis, the left eye was involved in 722 cases (49.8%), the right in 728 (50.2%).

Data from the 3,000 patients attending the Manchester Uveitis Clinic with all types of uveitis[5] also revealed that the majority of patients (61%) had chronic disease, either fluctuating (20.2%) or unremitting (41.0%). Around one-quarter of patients (25.2%) had a single acute episode and 13.6% had acute recurrent uveitis.

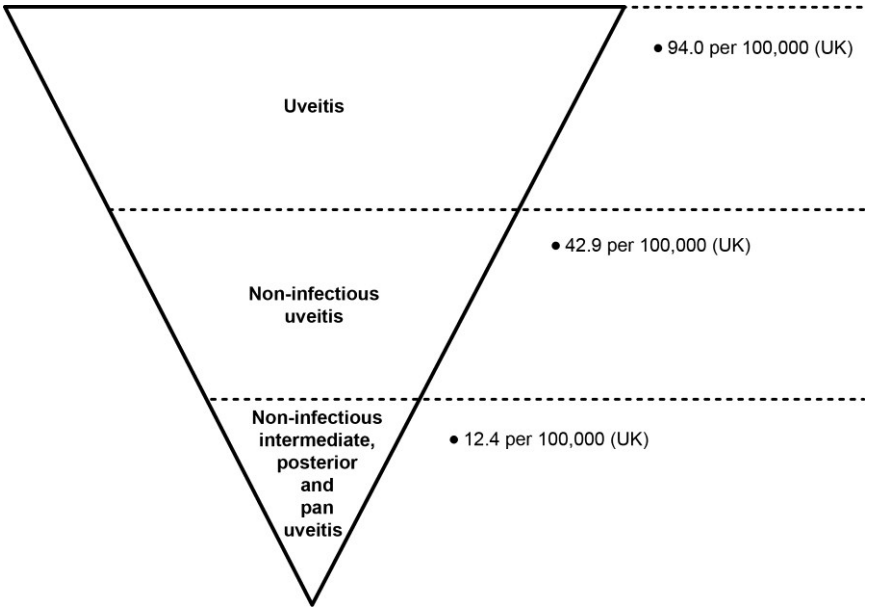
Prevalence

In the scope for this MTA, NICE states that non-infectious intermediate, posterior and pan uveitis account for around one-quarter of all uveitis cases[3]. NICE suggests that between 1,500 and 5,000 people are diagnosed with non-infectious intermediate or posterior uveitis each year in England. There are no data on the incidence of pan uveitis in England[3].

AbbVie carried out the EQUINOX study in 2012; the study used published epidemiological data to investigate the diagnosed prevalence of uveitis in the US and Europe[14]. Overall, estimates suggest that there are 94 cases per 100,000 of uveitis in the population aged over 18 years in the UK. Of

these 12.4 cases per 100,000 would be classified as non-anterior uveitis (1.6 per 100,000 intermediate, 7.0 per 100,000 posterior, 3.8 per 100,000 pan uveitis).

Figure 9: EQUINOX prevalence estimates of uveitis, intermediate, posterior and pan uveitis in the UK population per 100,000 adults.



Applying the UK-specific estimates from the EQUINOX study to the population of England suggests that there are currently 40,856 people with uveitis in England (94 per 100,000), of whom 13.2% have intermediate, posterior or pan uveitis disease which equates to 5,389 people. Posterior disease is the most common accounting for 56% of cases, followed by pan uveitis (31%) and intermediate uveitis (13%).

2.2 Treatment options

- The aim of treatment for all types of uveitis is to reduce inflammation, improve vision and prevent further deterioration of vision loss.
- Corticosteroids are the first-line treatment option for chronic non-infectious uveitis[3]. Treatment may be delivered topically as eye drops, locally as periocular or intravitreal injections or as an intravitreal implant or orally[1].
- Corticosteroids should be used with care because of the associated complications, related to the type, dose and duration of treatment, which include ocular complications (raised IOP and formation of cataract), osteoporosis, diabetes, susceptibility to infection, adrenal suppression and changes in mood and behaviour[1,15].
- Ocular damage increases with length of exposure to corticosteroids and delivery via injection or implant appears to carry a higher risk of damage than oral delivery[16].
- Systemic immunosuppression may be initiated second-line for patients in whom ocular inflammation has recurred on reducing the steroid dose or who have poorly controlled ocular inflammation with systemic steroids[1].
- Immunosuppressive treatment is begun early in the treatment of certain diseases—for example, posterior disease or pan uveitis associated with Behçet's syndrome, in which visual outcomes have been shown to be poor with corticosteroids alone[15].
- Many patients taking systemic drugs require a combination of two or more immunosuppressive agents, with or without corticosteroids, to control their ocular inflammation. It should be noted that most commonly used immunosuppressive agents used to treat uveitis are outside their product licence.
- Biologic agents are used third-line in patients who have not responded to or are unable to tolerate steroids and/or immunosuppressants[1].

The aim of treatment in uveitis is rapid resolution of ocular inflammation with restoration of vision. It is important to choose the drug and route of delivery to ensure penetration to the site of the ocular inflammation[1].

Corticosteroids are the first-line treatment option for chronic non-infective uveitis[3]. Treatment may be delivered topically as eye drops, locally as periocular or intravitreal injections or as an intravitreal implant or orally[1]. If patients have inflammation in the anterior part of the eye, topical steroids and pupil dilation may also be offered[3].

Corticosteroids should be used with caution because of the associated complications, related to the dose and duration of treatment. Indeed, international consensus is that drug-induced disease remission should be maintained with systemic corticosteroid doses below 10 mg prednisone daily[15]. Patients taking systemic corticosteroids for more than 3 weeks should be issued with a steroid treatment card and warned about the risks, which include susceptibility to infection, adrenal suppression and changes in mood and behaviour. Blood pressure and blood glucose concentrations should be measured at baseline and at intervals of 3 months. Patients who are taking or are likely to take corticosteroids for 3 months or longer should be assessed for their risk of osteoporosis and fracture and where necessary given prophylactic treatment, usually in the form of a bisphosphonate[1].

The use of corticosteroids is also associated with increased risk of ocular complications, which can potentially lead to vision loss. Damage increases with length of exposure to corticosteroids and delivery via injection or implant appears to carry a higher risk of damage than oral delivery. A systematic review and meta-analysis which included 50 studies of corticosteroids in all anatomical types of uveitis (22 clinical trials,16 chart reviews and 12 case series) was conducted to assess the impact of corticosteroids on ocular adverse events (AE)[16]. Of the studies, 30 studies assessed injection or implantable corticosteroids and the rest were either drops (n=8), oral (n=1) or a combination (n=11). The probability of an increase in IOP was greater as follow-up increased from 6 to 12 months and more common in patients receiving drops or injectable steroids (drops: 15% to 22%, injection: 29% to 40%, oral: 7% to 10%). The proportion (95% CI) of eyes that developed cataract was similar for injection [38% (27–49)] and oral [33% (20–45)] corticosteroids.

Systemic immunosuppression (e.g. methotrexate, mycophenolate mofetil, azathioprine (AZA), cyclosporine A and tacrolimus) may be initiated second-line for patients in whom ocular inflammation has recurred on reducing the steroid dose or who have poorly controlled ocular inflammation with systemic steroids. Immunosuppressive treatment is begun early in the treatment of certain diseases—for example, posterior disease or pan uveitis associated with Behçet's syndrome, in which visual outcomes have been shown to be poor with corticosteroids alone. The potential for side effects with immunosuppressive agents means that treatment must be individualised and regular monitoring performed[15]. It should be noted that the most commonly used immunosuppressive agents, such as methotrexate and AZA, are unlicensed for uveitis.

In practice, many patients taking systemic drugs require a combination of two or more immunosuppressive agents, with or without corticosteroids, to control the ocular inflammation. For those needing long-term treatment, the risks of systemic immunosuppression need to be weighed against the risks of systemic corticosteroids; for many patients a steroid-free regimen is preferable[1].

Biologics are used in patients who have not responded to or are unable to tolerate steroids and/or immunosuppressants[1]. Biologics may be used as steroid-sparing agents and can be used in combination with immunosuppressive agents[34].

2.3 NICE guidance and international treatment guidelines

- There is a paucity of guidelines for uveitis, particularly for intermediate, posterior and pan uveitis.
- Guidelines recommend corticosteroids first-line, followed by immunosuppressant therapy to allow a reduction in steroid dose or in those patients unable to tolerate or who fail to respond to steroids. Combination treatment is commonly used[15,34,35].
- Biologics are generally used third-line and have a role in treating sight-threatening uveitis refractory to conventional immunosuppression[34].
- Biologics may be used as steroid sparing agents or where other immunosuppressive agents are poorly tolerated as well as when ocular inflammation remains uncontrolled[35].
- In some specific patient groups with intermediate, posterior and pan uveitis and a poor prognosis, immunosuppression is used earlier in the treatment pathway[15].

There is a paucity of guidelines for uveitis, particularly for intermediate, posterior and pan uveitis disease and NICE have not produced guidance for uveitis. Most of the available guidance is in the form of recommendations rather than clinical guidelines.

Clinical management guidelines are available for anterior uveitis (acute and recurrent) from the College of Optometrists[36]. They recommend management with topical corticosteroids and pupil dilation with a mydriatic agent such as cyclopentolate. Patients with recurrent uveitis should be referred to an ophthalmologist.

NICE have recently recommended anti-TNF agents, including adalimumab (ADA), as an option for treating severe active AS and severe non-radiographic axial spondyloarthritis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs. Such patients often have extra-articular manifestations such as uveitis. It is acknowledged in the guidance that uveitis flares benefit from treatment with anti-TNF agents[37].

Guidance is available from Scotland, developed by the Scottish Uveitis Network. The Scottish Uveitis National Managed Clinical Network Treatment Guidelines were published in 2010 and focus on non-infectious uveitis[35]. Corticosteroids are first-line treatment, however, immunosuppression should be considered in patients requiring chronic steroid therapy >7.5 mg/day, in patients who relapse on steroid withdrawal or who fail to respond to steroids. The aim of immunosuppressant therapy is to allow a reduction in the steroid dosage while maintaining disease control. Most immunosuppressant drugs are well tolerated but all carry a small risk of severe side effects which may be potentially life-threatening. Biologics have a role in treating sight-threatening uveitis refractory to conventional immunosuppression. They may be used as steroid sparing agents or where other immunosuppressive agents are poorly tolerated as well as when ocular inflammation remains uncontrolled.

Immunosuppression is recommended in combination with corticosteroids as first-line treatment in patients with posterior uveitis, specifically ocular Behçet's disease, birdshot retinochoroidopathy, multifocal choroiditis with pan uveitis, serpiginous choroidopathy, Vogt-Koyangi-Harada disease and sympathetic ophthalmitis. These conditions have a poor prognosis if left untreated[35].

The Scottish guidance also includes information on the management of paediatric uveitis, which is most commonly due to JIA. Steroids are used cautiously in children and patients move to immunosuppression more rapidly than adults. Progress to a biologic is usual after the first second-line agent (an immunosuppressant) has failed.

Indeed, NHS England have commissioned ADA for children and adolescents with severe refractory anterior uveitis[19]. Criteria for commissioning are the presence of active anterior uveitis and failure to control uveitis with oral steroids (0.1 mg/kg/day of prednisolone) plus methotrexate plus topical steroid drops.

Elsewhere in Europe, guidance has been produced by professional bodies in Germany and the Netherlands. The European League Against Rheumatism (EULAR) have also published guidance on the management of Behçet's disease, which includes uveitis. The guidance is broadly similar to that issued in Scotland.

Table 4: European guidance for the treatment of uveitis

Country	Year	Patient group	First line	Second line	Third line
Germany	2001	Management of intermediate and posterior uveitis[38]	Corticosteroids	Immunosuppression	Anti-TNF
Germany	2010	Management of anterior uveitis[39]	Corticosteroids	Immunosuppression	Anti-TNF
Netherlands	2012	Addendum to guidelines for the diagnosis and treatment of uveitis[40]	Corticosteroids	Immunosuppression	Anti-TNF
EULAR	2009	Behçet's disease[41]	Immunosuppression	Biologics	

Recommendations have been produced by expert panels in the US focusing on the use of immunosuppressive drugs[15] and biologics[34] in uveitis.

Recommendations from 2000 on the use of immunosuppressive drugs, supports the use of immunosuppressant agents to minimise long-term corticosteroid use[15]. Immunosuppressive treatment should be begun early in the treatment of certain diseases—for example, posterior disease or pan uveitis associated with Behçet's syndrome, in which visual outcomes have been shown to be poor with corticosteroids alone.

The American Uveitis Society published recommendations for the use of biologics – specifically anti-TNF agents including ADA and infliximab in 2014[34]. Their recommendations are as follows: infliximab and ADA can be considered as corticosteroid sparing agents for the treatment of uveitis associated with Behçet's disease and as second-line immunomodulatory agents (after methotrexate) for the treatment of uveitis associated with juvenile arthritis. Infliximab (unlicensed indication) and ADA can be considered as potential second-line immunomodulatory agents for the treatment of severe ocular inflammatory conditions including posterior uveitis, pan uveitis, severe uveitis associated with seronegative spondyloarthropathy and scleritis in patients requiring immunomodulation in patients who have failed or who are not candidates for immunosuppression. Infliximab and ADA can be considered in these patients in preference to etanercept, which seems to be associated with lower rates of treatment success.

2.4 Adalimumab (Humira®)

- ADA is licensed for the treatment of non-infectious intermediate, posterior and pan uveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate[17].
- ADA reduces inflammation, it is a cytokine modulator or TNF-inhibitor and inhibits the activity of the pro-inflammatory cytokine tumour necrosis factor alpha (TNF-α) thereby reducing inflammation[17].
- ADA has been recommended as a treatment by NICE for a number of inflammatory conditions including rheumatoid arthritis, JIA, AS, psoriatic arthritis, plaque psoriasis, Hidradenitis suppurativa, Crohn's disease and ulcerative colitis[18].
- NHS England have commissioned ADA for children and adolescents with severe refractory anterior uveitis[19].
- The list price for 40 mg of ADA is £352.14[18].
- The recommended dose of ADA for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting 1 week after the initial dose[17].
- ADA can be self-administered outside the hospital, for example in the patient's home[17].

2.4.1 Licensed indications

This section outlines the licensed indications[17] for ADA beginning with uveitis, then lists all other relevant indications for which ADA has been licensed.

Uveitis

ADA is indicated for the treatment of non-infectious intermediate, posterior and pan uveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

Rheumatoid arthritis
ADA in combination with methotrexate, is indicated for:
- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

ADA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

ADA has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Juvenile idiopathic arthritis

Polyarticular JIA
ADA in combination with methotrexate is indicated for the treatment of active polyarticular JIA, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). ADA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enthesitis-related arthritis
ADA is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy.

Ankylosing spondylitis
ADA is indicated for the treatment of adults with severe active AS who have had an inadequate response to conventional therapy.

Axial spondyloarthritis without radiographic evidence of AS
ADA is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated C-reactive protein and/or MRI, who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs.

Psoriatic arthritis
ADA is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous DMARDs has been inadequate.

Plaque psoriasis
ADA is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

Paediatric plaque psoriasis
ADA is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Hidradenitis suppurativa (HS)
ADA is indicated for the treatment of active moderate to severe HS (acne inversa) in adult patients with an inadequate response to conventional systemic HS therapy.

Crohn's disease
ADA is indicated for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's disease
ADA is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy

including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis
ADA is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or AZA, or who are intolerant to or have medical contraindications for such therapies.

2.4.2 Mechanism of action

ADA (Humira) is a cytokine modulator or TNF-inhibitor; it inhibits the activity of the pro-inflammatory cytokine tumour necrosis factor alpha (TNF-α) and reduces inflammation.

TNF-α is produced primarily by activated monocytes/macrophages and plays a key role in inflammation. TNF-α acts via its receptors – TNF receptor 1, the major mediator of TNF-α action which initiates inflammatory responses and mediates apoptosis, and TNF receptor 2 which facilitates antiviral immune responses via cytotoxic T-lymphocytes[42].

ADA is a humanised bivalent mouse IgG1 monoclonal antibody, which binds specifically to TNF-α and blocks its interaction with both TNF receptor 1 and TNF receptor 2[42].

2.4.3 Presentation and cost

ADA in adults is available in the following presentations[18]:

- Humira 40 mg solution for injection in single-use pre-filled syringe (type I glass) with a plunger stopper (bromobutyl rubber) and a needle with a needle shield (thermoplastic elastomer).

- Humira 40 mg solution for injection in single-use pre-filled pen for patient use containing a pre-filled syringe. The syringe inside the pen is made from type 1 glass with a plunger stopper (bromobutyl rubber) and a needle with a needle shield (thermoplastic elastomer).

The list price for all presentations of ADA is £352.14 per 40 mg[18].

The recommended dose of ADA for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting 1 week after the initial dose[17].

It is recommended that the benefit and risk of continued long-term treatment with ADA should be evaluated on a yearly basis[17].

2.4.4 Concomitant therapy

Treatment with ADA for uveitis can be initiated in combination with corticosteroids and/or with other non-biologic immunomodulatory agents. Concomitant corticosteroids may be tapered in accordance with clinical practice starting 2 weeks after initiating treatment with ADA[17].

ADA is available for delivery to the patient's home. Patients or their carers can be trained in injection technique to allow ADA to be given at the patient's home. This reduces burden on NHS services and reduces the impact of receiving treatment on work productivity or activities of daily living for those who are not working. VAT is also not payable on any drug delivered outside the hospital setting[17].

3 Clinical evidence

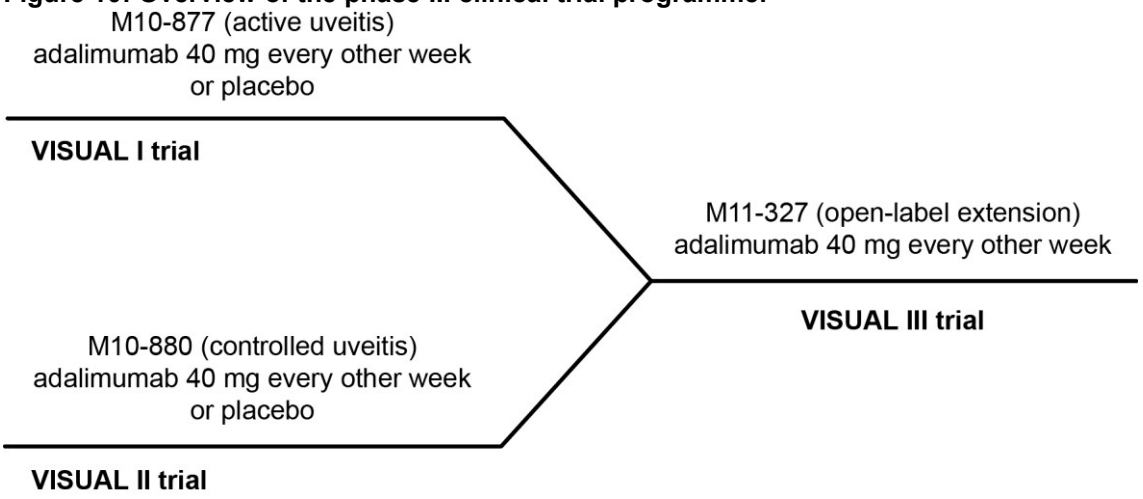
3.1 Overview of clinical evidence

- The phase III clinical trial programme for ADA in non-infectious intermediate, posterior and pan uveitis consists of two randomised controlled trials versus placebo (VISUAL I and VISUAL II) and an open label extension study including patients from both trials (VISUAL III).
- VISUAL I and II were similar in study design, however, VISUAL I included patients with active uveitis and the VISUAL II trial included patients with controlled disease.
- ADA was given as adjuvant treatment to corticosteroids, which were tapered during the study and a maximum of one concomitant immunosuppressive therapy from a choice of several options in both studies.

The phase III clinical trial programme for ADA in non-infectious intermediate, posterior and pan uveitis consists of two randomised controlled trials versus placebo (VISUAL I and VISUAL II) and an open label extension study including patients from both trials (VISUAL III).

VISUAL I and II were similar in study design, however, VISUAL I included patients with active uveitis, disease with current 'flare-ups' of symptoms and the VISUAL II trial included patients with uveitis controlled disease. ADA was given as adjuvant treatment to corticosteroids, which were tapered during the study and a maximum of one concomitant immunosuppressive therapy in both studies.

Figure 10: Overview of the phase III clinical trial programme.



The VISUAL I and VISUAL II studies have completed.

VISUAL I is accepted for publication in the *New England Journal of Medicine* without a designated publication date.

- Jaffe GJ, Dick AD, Brézin AP, et al. Adalimumab in Patients with Active Non-infectious Uveitis.

VISUAL II was published online in *The Lancet* on August 16th 2016[22].

- Nguyen QD, Merrill PT, Jaffe GJ, et al. Adalimumab for the prevention of uveitic flare in patients with inactive non-infectious uveitis requiring corticosteroids: a multicenter, double-masked, placebo-controlled phase 3, randomised controlled trial. *The Lancet* Published online August 16, 2016 http://dx.doi.org/10.1016/S0140-6736(16)31339-3

The results from VISUAL I and II have been presented at international conferences around the world.

We have used the Clinical Study Reports[20,21], the VISUAL II published paper[22] and presented posters, abstracts and presentations to inform this section.

VISUAL III is yet to report, some preliminary data will be presented in 2016 (International Uveitis Study Group meeting, Dublin). The meeting will be held 18-21st August 2016 and we have included information here for completeness.

3.2 VISUAL I and VISUAL II: study design

- The objective of VISUAL I and VISUAL II was to investigate the safety and efficacy of ADA compared with PBO in patients with non-infectious intermediate, posterior and pan uveitis in at least one eye, requiring high-dose systemic corticosteroids[20,21].
- VISUAL I and VISUAL II were phase III randomised, double-masked studies carried out worldwide[20,21].
- Patients in VISUAL I had active disease despite steroid use (n=217) and those in VISUAL II had controlled disease whilst receiving steroids (n=226)[20-22].
- The studies ended when a defined number of treatment failures had occurred (138 in VISUAL I and 106 in VISUAL II)[20,21].
- The primary end-point for both trials was time to treatment failure which was a composite end-point made up of four criteria which assessed ocular inflammation (AC cell grade and VH grade), lesion formation and visual acuity[21,22].
- Secondary end-points included measures of ocular inflammation, visual acuity, macular oedema and VRQOL[21,22].
- Control of disease was assessed by measuring quiescence and steroid-free quiescence[20,21].
- QOL, anxiety and depression, work productivity and activity and healthcare resource use (HRU) were also assessed[20,21].

The objective of VISUAL I and VISUAL II was to investigate the safety and efficacy of ADA with PBO in patients with non-infectious intermediate, posterior and pan uveitis in at least one requiring high-dose systemic corticosteroids. The two studies were similar in design as shown in Table 5, Figure 11 and
Figure 12.

Table 5: Overview of VISUAL I and VISUAL II[20-22].

Study name	**VISUAL I (M10-877)**	**VISUAL II (M10-880)**
Locations	102 centres in Australia, Europe, Israel, Latin America, North America 14 patients from the UK	102 centres in Australia, Europe, Israel, Latin America, North America 18 patients from the UK
Duration	Study ended when 138 treatment failures had occurred	Study ended when 106 treatment failures had occurred
Study type	Phase III double-masked randomised, placebo-controlled	
Study drugs	Treatment: ADA 80 mg loading dose at week 1/ ADA 40 mg every other week (EoW) administered as a subcutaneous (SC) injection Placebo: matching placebo administered as a SC injection as per ADA	
Prednisone	Mandatory 60 mg/day burst at week 0 taper to discontinuation at week 15	10-35 mg/day tapered to discontinuation at week 19 based on the dose of prednisone at baseline
Concomitant drugs	Topical corticosteroids were allowed at baseline but were tapered and discontinued by week 9 Patients could receive one of the following immunosuppressants: methotrexate, cyclosporine, mycophenolate mofetil or an equivalent drug to mycophenolate mofetil (e.g. mycophenolic acid), AZA or tacrolimus	
Number of patients	217 110 randomised to ADA 107 randomised to PBO	226 115 randomised to ADA 111 randomised to PBO
Patients	Adults with a diagnosis of non-infectious intermediate, posterior and pan uveitis in at least one eye with previous adequate response to oral corticosteroids and **active** disease	Adults with a diagnosis of **controlled** non-infectious intermediate, posterior and pan uveitis in at least one eye requiring chronic corticosteroid therapy ≥10 mg /day to control their disease Patients also had to be taking oral prednisone 10–35 mg/day at baseline to ensure their dependency on corticosteroid use to maintain controlled disease
Primary end-point	Time to treatment failure, defined as	Time to treatment failure, defined by the

	worsening of at least one of the following criteria compared to baselines: inflammatory chorioretinal and/or inflammatory retinal vascular lesions, AC cell grade, VH grade, best corrected visual acuity (BCVA)	occurrence of a uveitis flare (inability to maintain disease control) Defined as **presence** of at least one of the following criteria compared to baselines: inflammatory chorioretinal and/or inflammatory retinal vascular lesions, AC cell grade, VH grade, BCVA
Study visits	Baseline, weeks 1, 4, 6, 8 and every 4 weeks thereafter (week 27 not week 28)	Baseline, weeks 2, 4, 6, 8 and every 4 weeks thereafter (week 27 not week 28)

Figure 11: Study design for VISUAL I[21].

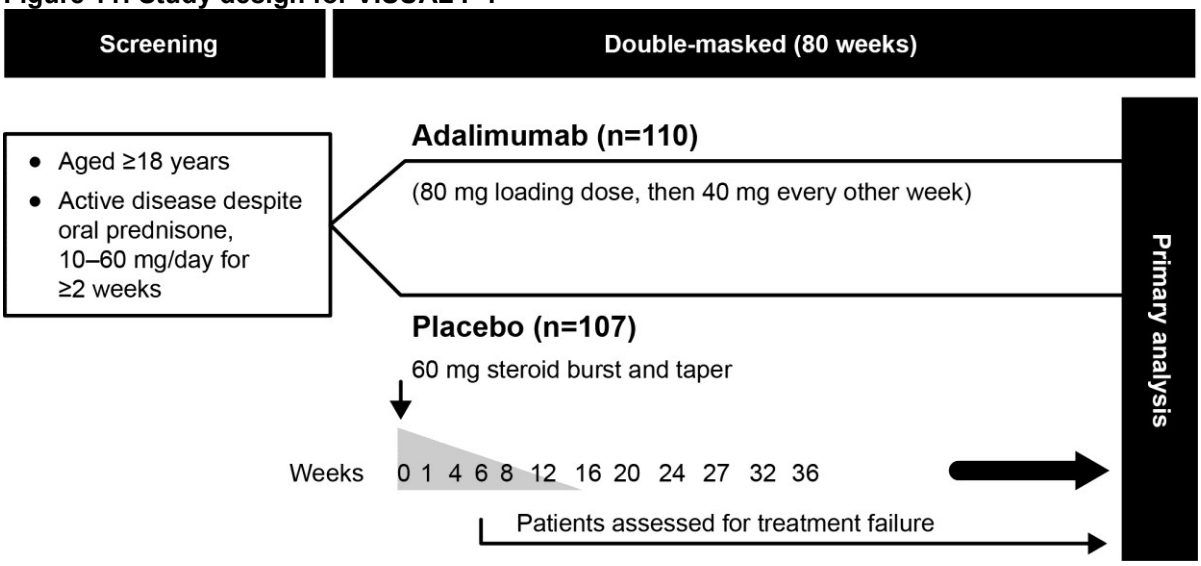
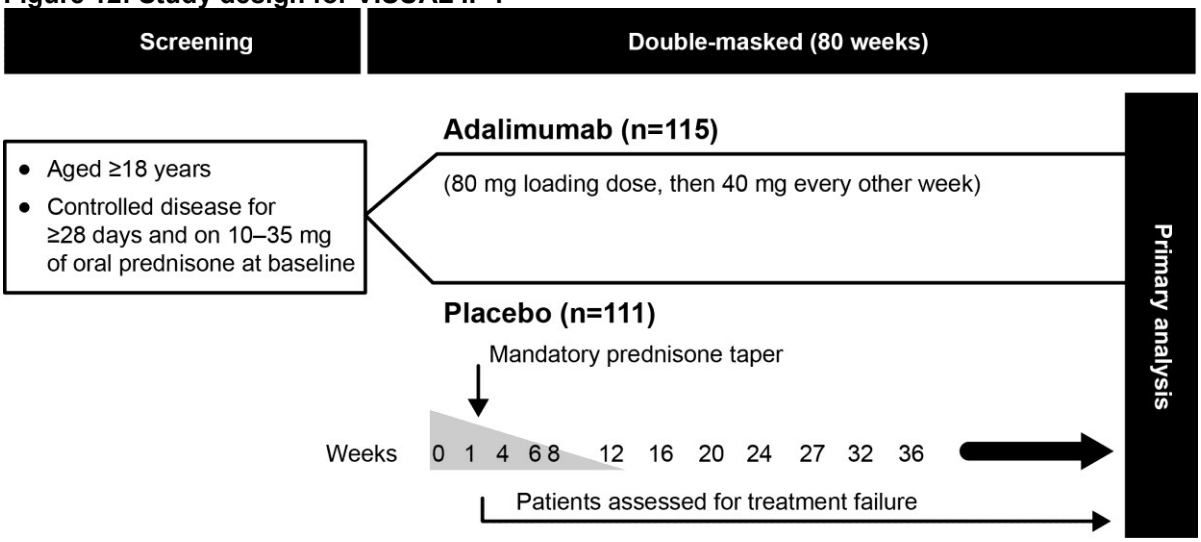


Figure 12: Study design for VISUAL II[43].



3.2.1 Randomisation and masking

Patients were randomised to treatment in a 1:1 double-masked fashion using an Interactive Web and Voice Response System (IVRS/IWRS) using baseline immunosuppressant treatment as a stratification factor.

All AbbVie personnel with direct oversight of the conduct and management of the study (with the exception of the AbbVie Drug Supply Management Team), the investigator, study site personnel and the patient remained blinded to treatment throughout the study.

3.2.2 Inclusion and exclusion criteria

Inclusion and exclusion criteria are shown below in Table 6 – the key differences are that patients in VISUAL I had active disease despite steroid use and those in VISUAL II had controlled disease whilst receiving steroids.

Table 6: Inclusion and exclusion criteria[20-22].

Study name	VISUAL I (M10-877)	VISUAL II (M10-880)
Inclusion	Adult patients aged 18 years and over with active non-infectious intermediate, posterior and pan uveitis	Adult patients aged 18 years and over with controlled non-infectious intermediate, posterior and pan uveitis
	Patients must have active disease at the baseline visit defined by the presence of **at least one** of the following parameters in at least one eye despite ≥2 weeks of maintenance therapy with oral prednisone at a dose of ≥10 mg/day to ≤60 mg/day (or oral corticosteroid equivalent): • Active, inflammatory, chorioretinal and/or inflammatory retinal vascular lesion • ≥2+ AC cells grade (SUN criteria) • ≥2+ VH grade (NEI/SUN criteria)	Patients with controlled disease for >28 days prior to baseline and taking ≥10 mg of oral prednisone and **all three** of the following criteria at screening and baseline • Without active, inflammatory chorioretinal and/or inflammatory retinal vascular lesion • AC cell grade ≤0.5+ (SUN criteria) • VH grade ≤0.5+ (NEI/SUN criteria)
	Patient on oral prednisone at a dose of ≥10 mg/day to ≤60 mg/day (or oral corticosteroid equivalent) for at least 2 weeks prior to screening and remained on the same dose from screening to baseline visit	Patient on oral prednisone at a dose of ≥10 mg/day to ≤35mg/day (or oral corticosteroid equivalent) at baseline and remained on the same dose from screening to baseline visit
	Documented prior adequate response to oral corticosteroids (equivalent of oral prednisone up to 1 mg/kg/day)	History of at least one disease flare within 18 months of the screening visit. Flare should be during or within 28 days of tapering oral corticosteroid therapy
	No previous, active or latent TB	
Exclusion	Isolated anterior uveitis	
	Confirmed or suspected infectious uveitis	
	Previous exposure to anti-TNF therapy or any biologic therapy (except intravitreal anti-VEGF therapy) with a potential therapeutic impact on non-infectious uveitis	
	Prior inadequate response to high-dose oral corticosteroids	
	On more than one immunosuppressive therapy (not including corticosteroids) at baseline	On more than one immunosuppressive therapy (not including corticosteroids) within 28 days prior to baseline
	On concomitant immunosuppressive therapy other than methotrexate, cyclosporine, mycophenolate mofetil or an equivalent drug to mycophenolate mofetil (e.g. mycophenolic acid), AZA or tacrolimus at baseline	On concomitant immunosuppressive therapy other than methotrexate, cyclosporine, mycophenolate mofetil or an equivalent drug to mycophenolate mofetil (e.g. mycophenolic acid), AZA or tacrolimus within 28 days of baseline
	Intraocular or periocular corticosteroids within 30 days prior to the baseline visit	Intraocular or periocular corticosteroids within 90 days prior to the baseline visit
	Severe VH grade that precludes visualisation of the fundus at the Baseline visit	CMO unless the retinal changes are persistent, residual and stable as defined by the SUN criteria (persistent is >3 months duration)

3.2.3 End-points

Primary end-point

The primary end-point for both trials was time to treatment failure which was a composite end-point made up of four criteria.

- In VISUAL I the primary end-point was time to treatment failure defined as worsening of at least one of the criteria on or after week 6.

- In VISUAL II the primary end-point was time to treatment failure defined as presence of at least one of the criteria on or after week 2.

The criteria are outlined below:

- Inflammatory, chorioretinal and/or retinal vascular lesions which provides a measure of inflammation.

- AC cell grade which provides a measure of inflammation in the AC, where an increase in the number of AC cells may reduce visual function.

- VH grade which provides a measure of inflammation in the vitreous, where a higher VH grade may lead to increasingly blurred vision.

- Visual acuity (based on the Early Treatment of Diabetic Retinopathy Study [ETDRS] scale). The ETDRS chart is a commonly used measure of visual acuity in clinical trials and is based on the logarithm of the Minimal Angle of Resolution (logMAR) scale measuring visual acuity loss. Positive values indicate vision loss, while negative values denote normal or improved visual acuity.

Table 7: Treatment failure criteria in VISUAL I and VISUAL II[20-22].

	VISUAL I		**VISUAL II**
	Treatment failure criteria – at least one must be present in either eye		
Criteria	Week 6 visit	All other visits after week 6	At or at week 2
Inflammatory, chorioretinal and/or retinal vascular lesions	New active, inflammatory lesions relative to baseline		New active, inflammatory lesions relative to baseline
AC cell grade	Inability to achieve ≤0.5+	2-step increase relative to best state achieved	2-step increase relative to baseline
VH grade	Inability to achieve ≤0.5+	2-step increase relative to best state achieved	2-step increase relative to baseline
Visual acuity	Worsening of BCVA by ≥15 letters relative to best state achieved		Worsening of BCVA by ≥15 letters relative to baseline

In comparison to the end-points of similar trials of ocular treatments (usually VH grading alone) this composite end-point allows a more stringent measure of visual functioning. The four criteria used to assess treatment failure include well established and defined measures of ocular inflammation (AC cell grade and VH grade), absence of new lesions and an additional measure of visual acuity.

The four criteria reflect the real world complexity of the disease using clinically meaningful flare measures. Indeed data from a study which assessed the relationship between clinician-assessed treatment failure in VISUAL I and VISUAL II and patient reported changes in VRQOL using VFQ-25 found that in both studies treatment failure, as defined in the clinical trials, was associated with clinically meaningful decreases in VFQ-25. Thus supporting treatment failure as a relevant outcome from the patients' perspective[45].

Secondary end-points

Secondary end-points were common to both studies, although the timing of assessments varied. Due to the initial steroid burst in VISUAL I assessment was relative to the best state achieved prior to week 6, whereas in VISUAL II assessment was relative to baseline.

The secondary end-points were ranked as shown in Table 8.

Table 8: Secondary end-points in VISUAL I and VISUAL II[20,21].

Rank	End-point	Details of end-point	VISUAL I	VISUAL II
1	Change in AC cell grade in each eye	Measures inflammation in the AC, an increase in the number of AC cells may reduce visual function	From best state achieved prior to week 6 to the final/early termination visit.	From baseline to the final/early termination visit.
2	Change in VH grade (NEI/SUN criteria) in each eye	Measures inflammation in the vitreous, a higher VH grade may lead to increasingly blurred vision		
3	Change in logarithm of the minimum angle of resolution (logMAR) BCVA	Measures visual acuity		
4	Time to ocular coherence tomography (OCT) evidence of macular oedema	Measures macular oedema a major cause of vision loss The study assessed macular oedema in a subset of patients without macular oedema at baseline	On or after week 6.	On or after week 2.
5	Percentage change in central retinal thickness (CRT) in each eye		From best state achieved prior to week 6 to the final/early termination visit.	From baseline to the final/early termination visit
6	Change in VFQ-25 composite score	Measures VRQOL Questionnaire of 11 vision related subscales. Each subscale is scored from 0–100, where 0 represents the lowest visual functioning and 100 indicates the best possible visual functioning. A minimally important difference for VFQ is defined as a change of 3.86 for the total score and 5–10 points for the domain scores		
7	Change in VFQ-25 distance vision subscale	Measures distance vision		
8	Change in VFQ-25 near vision subscale	Measures near vision		
9	Change in VFQ-25 ocular pain subscale	Measures eye pain		

In VISUAL I, two *post hoc* analyses were carried out to assess the impact of ADA on macular oedema.

- Time to OCT evidence of macular oedema in at least one eye on or after week 6 in patients without macular hole and/or retinal detachment.

- Percentage change in CRT in each eye from best state achieved prior to week 6 to the final/ early termination visit (LOCF) in patients without macular hole and/or retinal detachment.

Disease quiescence

Quiescence, defined as patients with no new active inflammatory lesions and having AC cell and VH grade of ≤0.5+ was used to assess activity of disease.

Steroid-free quiescence, was defined as lack of inflammation (no active inflammatory lesions and AC cell grade = 0 and VH grade = 0) whilst not receiving steroids.

The proportion of patients in steroid-free quiescence at each visit was reported from weeks 16–52 for VISUAL I and from weeks 20–52 for VISUAL II clinical trials after the end of the mandatory prednisone taper[46].

Patient reported outcomes

PROs were assessed using the following scales:

- VFQ-25 subscores; the 11 VFQ-25 subscores include general health, general vision, ocular pain, near activities, distance activities, vision specific social functioning, vision specific mental health, vision specific role difficulties, vision specific dependency, driving, colour vision and peripheral vision.
- Hospital Anxiety and Depression Scale (HADS), measures anxiety and depression.
- Work Productivity and Activity Impairment Questionnaire (specific health problem) (WPAI-SHP), measures impact on work and activity.
- EuroQol five dimensions questionnaire (EQ-5D), measures QOL.
- HRU.

3.2.4 Statistical analysis

All randomised patients were included in an intention-to-treat (ITT) set and the safety set consisted of all patients who received at least one dose of the study drug (PBO and ADA). No per protocol analysis was planned.

The primary end-point (time to treatment failure) was calculated using Kaplan-Meier estimates and was compared using a log-rank test at a 2-sided significance level of 5%.

Treatment failures were counted as events and dropouts, due to reasons other than treatment failure, were considered as censored observations at the time of dropout.

The secondary end-points (except time to OCT evidence of macular oedema which was calculated as per the primary end-point) were analysed using ANOVA adjusted for clustered observations (i.e. observations from each eye) for the clinical outcomes and using ANOVA for VFQ-25. Missing values were imputed using the last observation carried forward (LOCF).

In VISUAL I, sample size was based on a PBO treatment failure rate at 6 months of 42.5% and an ADA failure rate of 27.5%. For conservative purposes it was assumed that failures would begin after 2 months on study as the prednisone dose tapered down. In addition a pooled dropout rate of 35% over 12 months was assumed. Using these failure rate assumptions for a log-rank test and a 2-sided significance level of 5%, a total of 138 treatment failures were needed. The assumptions also included the following power of 90% and average accrual rate of four patients per month in the first 30 months and seven per month thereafter.

In VISUAL II, sample size was based on a PBO treatment failure rate at 6 months of 70% and an ADA failure rate of 50%. For conservative purposes it was assumed that failures would begin after 2 months on study as the prednisone dose tapered down. In addition a pooled dropout rate of 35% over 12 months was assumed. Using these failure rate assumptions for a log-rank test and a 2-sided significance level of 5%, a total of 84-107 treatment failures were needed. The assumptions also included the following power of 80% and average accrual rate of three patients per month in the first 28 months and 16 per month thereafter.

3.3 VISUAL I and VISUAL II: Patient flow and characteristics

- In both studies more patients receiving ADA completed the study than patients receiving PBO[20,21].
- Patients were well matched across treatment groups in VISUAL I and VISUAL II[21,22].
- Most patients were female (around 60%), were white (around 80%) and aged in their early 40s across both studies[21,22].
- Pan uveitis was the most common form of uveitis accounting for 45% of cases, followed by posterior and intermediate. The cause of uveitis was idiopathic in around one-third of cases, with autoimmune conditions accounting for the balance. Both eyes were affected in >90% of cases[21,22].

- Around one-third (30%) of patients were taking concomitant immunosuppressants in VISUAL I and around one-half (47%) in VISUAL II. Methotrexate and mycophenolate mofetil or equivalent were the most commonly taken agents[20,21].

3.3.1 Patient flow

The patient flow is shown in Table 9, by definition patients who reached week 80 without treatment failure or had to discontinue the study because the planned number of treatment failures was reached were considered completers.

As the primary efficacy end-point for VISUAL I was time to treatment failure on or after week 6, patients were not considered to have prematurely discontinued if they discontinued due to treatment failure after week 6. In VISUAL I, 48 patients completed the study, 144 discontinued due to treatment failure and 25 discontinued prematurely due to AE, lack of efficacy, withdrawal of consent and loss to follow-up. More patients in the ADA arm completed the study (32 versus 16) or discontinued prematurely (18 versus 7) and more patients in the PBO arm experienced treatment failure (84 versus 60).

As the primary efficacy end-point for VISUAL II was time to treatment failure on or after week 2, patients were not considered to have prematurely discontinued if they discontinued due to treatment failure after week 2. In VISUAL II, 90 patients completed the study, 106 discontinued due to treatment failure and 30 discontinued prematurely. More patients in the ADA arm completed the study (56 versus 34) and more patients in the PBO arm experienced treatment failure (61 versus 45) or discontinued prematurely (16 versus 14).

Table 9: Patient flow in VISUAL I and VISUAL II[20-22].

	VISUAL I (ITT)			VISUAL II (ITT)		
	PBO n=107	ADA n=110	Total n=217	PBO n=111	ADA n=115	Total n=226
Completed the study	16 (14.9%)	32 (29.0%)	48 (22.1%)	34 (30.6%)	56 (48.7%)	90 (39.5%)
Treatment failure	84 (78.5%)	60 (54.5%)	144 (66.4%)	61 (54.9%)	45 (39.1%)	106 (46.9%)
Premature discontinuation	7 (6.5%)	18 (16.4%)	25 (11.5%)	16 (14.4%)	14 (12.2%)	30 (13.3%)
AE	3 (2.8%)	10 (9.1%)	13 (6.0%)	7 (6.3%)	10 (8.7%)	17 (17.5%)
Lack of efficacy	2 (1.9%)	1 (0.9%)	3 (1.4%)	3 (2.7%)	0	3 (1.3%)
Withdrawal of consent	0	2 (1.8%)	2 (0.9%)	3 (2.7%)	2 (1.7%)	5 (2.2%)
Loss to follow up	0	4 (3.6%)	4 (1.8%)	3 (2.7%)	0	3 (1.3%)
Other	3 (2.8%)	5 (4.5%)	8 (3.7%)	3 (2.7%)	2 (1.7%)	5 (2.2%)

3.3.2 Baseline demographic characteristics

The baseline characteristics of patients in VISUAL I and VISUAL II are summarised in Table 10. Most patients were female (around 60%), were white (around 80%) and aged in their early 40s across both studies.

In both studies, patients were well matched across treatment groups.

Pan uveitis was the most common form of uveitis accounting for 45% of cases, followed by posterior and intermediate. The cause of uveitis was idiopathic in around one-third of cases, with autoimmune conditions accounting for the balance. Both eyes were affected in >90% of cases.

Around one-third (30%) of patients were taking concomitant immunosuppressants in VISUAL I and around one-half (47%) in VISUAL II. Methotrexate and mycophenolate mofetil or equivalent were the most commonly taken agents.

In VISUAL I more patients experienced two or more flares than in VISUAL II, however, the time since the last flare was longer in VISUAL I than in VISUAL II reflecting that patients in VISUAL I had active disease.

Table 10: Baseline characteristics in VISUAL I and VISUAL II, ITT Analysis Sets[20-22].

	VISUAL I			VISUAL II		
Parameter	PBO n=107	ADA n=110	Total n=217	PBO n=111	ADA n=115	Total n=226
Sex, Female; n (%)	65 (60.7%)	59 (53.6%)	124 (57.1%)	72 (64.9%)	66 (57.4%)	138 (61.1%)
Race, White; n (%)	86 (80.4%0	88 (80.0%)	174 (80.2%)	93 (83.8%)	96 (83.5%)	186 (82.3%)
Age, yrs; mean ± SD	42.6 ± 14.2	42.7 ± 15.6	42.7 ± 14.9	42.2 ± 14.0	42.8 ± 12.9	42.6±13.4
Type of uveitis, n (%)*						
Intermediate	23 (21.5%)	24 (21.8%)	47 (21.7%)	30 (27.0%)	17 (14.8%)	47 (20.8%)
Posterior	37 (34.6%)	36 (32.7%)	73 (33.6%)	34 (30.6%)	39 (33.9%)	73 (32.3%)
Pan uveitis	47 (43.9%)	50 (45.5%)	97 (44.7%)	46 (41.4%)	57 (49.6%)	103 (45.6%)
Intermediate/posterior				1 (0.9%)	2 (1.7%)	3 (1.3%)
Diagnosis, n (%)						
Idiopathic	45 (42.1%)	36 (32.7%)	81 (37.3%)	40 (36.0%)	29 (25.2%)	69 (30.5%)
Birdshot choroidopathy	20 (18.7%)	24 (21.8%)	44 (20.3%)	15 (13.5%)	15 (13.0%)	30 (13.3%)
Multifocal choroiditis and pan uveitis	3 (2.8%)	8 (7.3%)	11 (5.1%)	2 (1.8%)	5 (4.3%)	7 (3.1%)
Vogt-Koyanagi-Harada	14 (13.1%)	11 (10.0%)	25 (11.5%)	25 (22.5%)	26 (22.6%)	51 (22.6%)
Sarcoid	8 (7.5%)	10 (9.1%)	18 (8.3%)	14 (12.6%)	18 (15.7%)	32 (14.2%)
Behçet's	4 (3.7%)	12 (10.9%)	16 (7.4%)	6 (5.4%)	10 (8.7%)	16 (7.1%)
Other	13 (12.1%)	9 (8.2%)	22 (10.1%)	9 (8.1%)	12 (10.4%)	21 (9.3%)
Eye affected, n (%)						
Left	5 (4.7%)	5 (4.5%)	10 (4.6%)	3 (2.7%)	2 (1.7%)	5 (2.2%)
Right	3 (2.8%)	7 (6.4%)	10 (4.6%)	4 (3.6%)	1 (0.9%)	5 (2.2%)
Both	99 (92.5%)	89 (89.1%)	197 (90.8%)	104 (93.7%)	112 (97.4%)	216 (95.6%)
Number of flares in the past 12 months, n (%)						
1	19 (17.8%)	18 (16.4%)	37 (17.1%)	46 (41.4%)	48 (41.7%)	94 (41.6%)
2	46 (43.0%)	54 (49.1%)	100 (46.1%)	40 (36.0%)	43 (37.4%)	83 (36.7%)
3	42 (39.3%)	38 (34.5%)	80 (36.9%)	25 (22.5%)	24 (20.9%)	49 (21.7%)
Time since last flare (mean months)	10.0 ± 14.9	10.3 ± 17.2	10.2 ± 16.1	5.1 ± 3.9	5.6± 3.8	5.4 ± 3.9
Concomitant immunosuppressant, n (%)						
AZA	4 (3.7%)	4 (3.6%)	8 (3.7%)	11 (9.9%)	3 (2.6%)	14 (6.2%)
Cyclosporine	3 (2.8%)	10 (9.1%)	13 (6.0%)	11 (9.9%)	15 (13.0%)	26 (11.5%)
Methotrexate	12 (11.2%)	9 (8.2%)	21 (9.7%)	14 (12.6%)	19 (16.5%)	33 (14.6%)
Mycophenolate mofetil or equivalent	14 (13.1%)	11 (10.0%)	25 (11.5%)	17 (15.3%)	17 (14.3%)	34 (15.0%)

3.4 VISUAL I: efficacy results

- In VISUAL I, the median time to treatment failure was 24 weeks (5.6 months) in the ADA group and 13 weeks (3 months) in the PBO group[21].
- Patients receiving ADA were significantly ($p<0.001$) less likely to experience treatment failure than the PBO group: HR was 0.5 (95% CI: 0.36–0.70)[21].
- Each of the four components of the primary end-point showed significant benefit with ADA over PBO[21].
- The use of permitted concomitant immunosuppressants did not significantly alter the time to treatment failure in either the ADA or PBO group[21].
- The secondary end-points demonstrated significant benefit in visual acuity, inflammation, macular oedema and VRQOL (total score, ocular pain, near vision) with ADA compared with PBO[21].
- The proportions of patients in quiescence and steroid-free quiescence were significantly higher in the ADA group compared to PBO at all scheduled visits with the exception of week 6 and week 12[21].
- There was a significant improvement in HRQOL (as measured by EQ-5D), in mental health (as measured by a subscale of VFQ-25) and a reduction in work time lost as measured on the WPAI in patients receiving ADA compared to those receiving PBO[21].

3.4.1 Primary end-point

The primary end-point was a composite made up of measures of inflammation and visual acuity (inflammatory, chorioretinal and/or retinal vascular lesions, AC cell grade, VH grade and visual acuity).

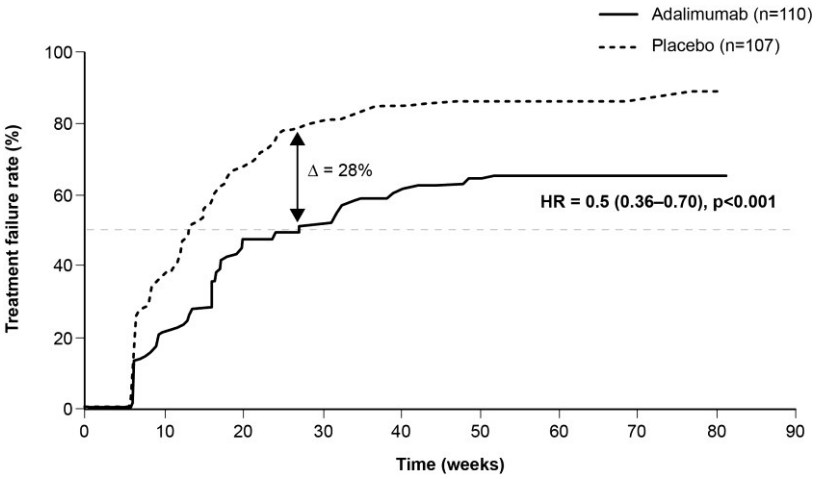
In VISUAL I the primary end-point was time to treatment failure defined as worsening of at least one of the criteria on or after week 6.

Data on the primary end-point has been presented at international conferences, we have used data presented at the American College of Rheumatology (ACR) in 2015[24] to inform this section, together with the CSR[21].

The median time to treatment failure was 24 weeks (5.6 months) in the ADA group and 13 weeks (3 months) in the PBO group. With a HR of 0.5 (95% CI: 0.36–0.70), patients receiving ADA were significantly (p<0.001) less likely to experience treatment failure than the PBO group.

A clear separation was seen between the two groups from week 6 onwards. At this time in the study all patients were receiving 15 mg/day prednisone, a dose too high to sustain in long-term treatment.

Figure 13: Time to treatment failure in VISUAL I[24].



Analysis of time to treatment failure once stratified for the use of permitted immunosuppressant therapies showed no significant difference in HR compared to the primary analysis (Table 11), showing that the use of permitted concomitant immunosuppressants did not significantly alter the time to treatment failure in either the ADA or PBO group.

Table 11: Time to treatment failure at or after week 6, adjusted for immunosuppressant use at baseline in VISUAL I[21].

	Treatment failure n (%)	Median time to treatment failure	HR	p value
PBO (n=107)	84 (78.5%)	3.0	0.5 (0.36,0.70)	<0.001
ADA (n=110)	60 (54.4%)	6.0		

The components of the composite end-point were also assessed, all of which showed significant benefit in the ADA arm, see Figure 14 to Figure 17.

Figure 14: Treatment failure due to development of new inflammatory lesions in VISUAL I[24].

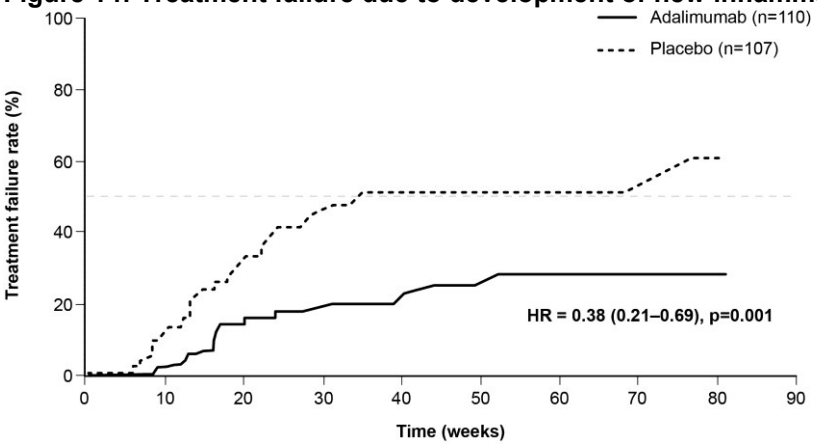


Figure 15: Treatment failure due to worsening of AC cell grade in VISUAL I[24].

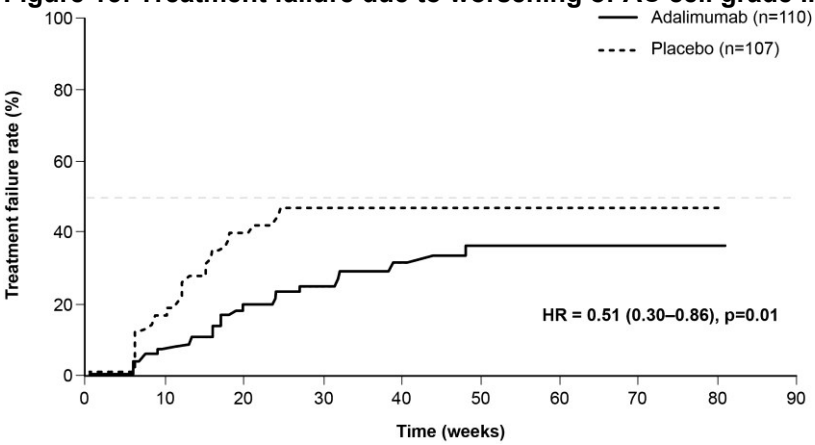


Figure 16: Treatment failure due to worsening of VH grade in VISUAL I[24].

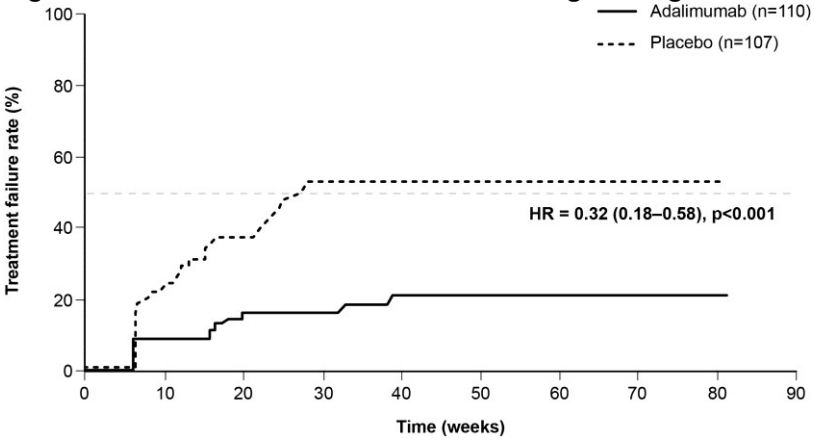
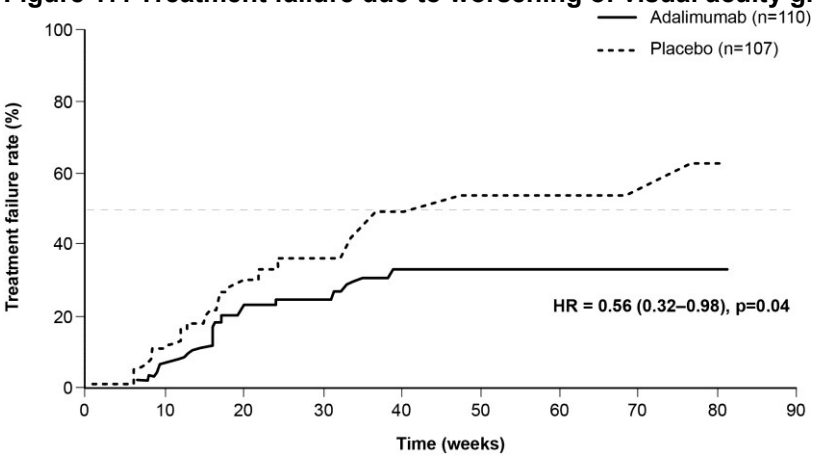
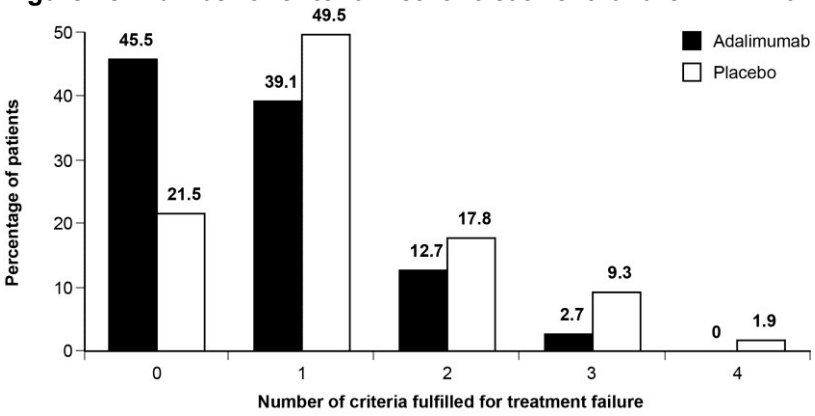


Figure 17: Treatment failure due to worsening of visual acuity grade in VISUAL I[24].



The number of reasons met for treatment failure was higher for the placebo group compared with the ADA group, see Figure 18. Of the four pre-specified reasons for treatment failure, the largest difference for treatment failure was in VH grade (14.5% and 36.4% for ADA and PBO groups, respectively).

Figure 18: Number of criteria met for treatment failure in ADA and PBO arms[21].



Taken together patients on PBO had a significantly shorter time to flare, furthermore, more PBO-treated patients flared based on multiple flaring criteria compared with ADA.

3.4.2 Secondary end-points: clinical

The clinical secondary end-points are shown in Table 12. All showed significant benefit with ADA versus PBO except time to evidence of macular oedema. However, pre-specified *post hoc* analyses in patients without macular hole and/or retinal detachment demonstrated that ADA did confer significant benefit over PBO, see Table 13.

Table 12: Ranked clinical secondary end-points in VISUAL I[24].

Ranked secondary end-points*	PBO (n=107)		ADA (n=110)		
	n	Mean	n	Mean	p value
1. Change in AC cell grade					
Left eye	102	0.59	101	0.35	
Right eye	102	0.69	101	0.36	
Difference, mean (95% CI)	-0.29 (-0.51 to -0.07)				0.011†
2. Change in VH grade					
Left eye	103	0.33	101	0.11	
Right eye	103	0.45	101	0.13	
Difference, mean (95% CI)	-0.27 (-0.43 to -0.11)				<0.001†
3. Change in BCVA, logMAR					
Left eye	103	0.12	101	0.07	
Right eye	103	0.13	101	0.04	
Difference, mean (95% CI)	-0.07 (-0.11 to -0.02)				0.003†
4. Time to evidence of CMO on or after week 6 (patients without CMO at baseline) [Pre-specified analysis]					
Median	45	6.2	55	11.1	
HR (95%CI)	0.70 (0.39 to 1.26)				0.231‡
5. Percentage change in CRT [Pre-specified analysis]					
Left eye	100	20.2	100	9.6	
Right eye	102	22.0	101	8.2	
Difference, mean (95% CI)	-11.4 (-20.9 to -1.8)				0.020‡
†p value from analysis of variance with treatment as a factor and adjusted for clustered observations. ‡2-sided p value from log rank test. *Unless otherwise noted, data reflect change from best state achieved prior to week 6 to the final or early termination visit.					

Table 13: *Post-hoc* analyses of macular oedema end-points in VISUAL I[24].

	PBO (n=107)		ADA (n=110)		
***Post-hoc* analyses**	**n**	**Mean**	**n**	**Mean**	**p value**
4. Time to OCT evidence of macular oedema (thickening of CRT) on or after week 6 (only in patients without MO based on CRT at baseline and without macular hole and/or retinal detachment)					
Median	71	NE	72	NE	
HR (95% CI)	0.33 (0.12 to 0.90)				0.023‡
5. Percent change in CRT					
Left eye	100	20.2	99	8.5	
Right eye	102	22.0	100	8.0	
Difference, mean (95% CI)	-12.0 (-21.5 to -2.5)				0.014#

‡2-sided p value from log rank test. *Unless otherwise noted, data reflect change from best state achieved prior to week 6 to the final or early termination visit. #p value from analysis of variance with treatment and OCT machine as factors and adjusted for clustered observations.
NE: not estimable

3.4.3 Secondary end-points: VRQOL

The ranked secondary end-points which considered VRQOL also showed benefit with ADA over PBO. Significant and meaningful benefit was seen in the total (composite) score and in near vision and ocular pain. Significant improvements were also seen in general vision and mental health, although these were not pre-specified secondary end-points. Table 14 lists the results and Figure 19 shows change in VFQ-25 composite score over time.

In the VFG-25 scale, 0 represents the lowest visual functioning and 100 indicates the best possible visual functioning, Figure 19 indicates that mean VFQ-25 total scores for ADA and PBO were similar throughout the 6 week tapering period, but subsequently diverged, maintaining separation through to week 80. Throughout this period, patients receiving ADA had improved VRQOL over those on PBO.

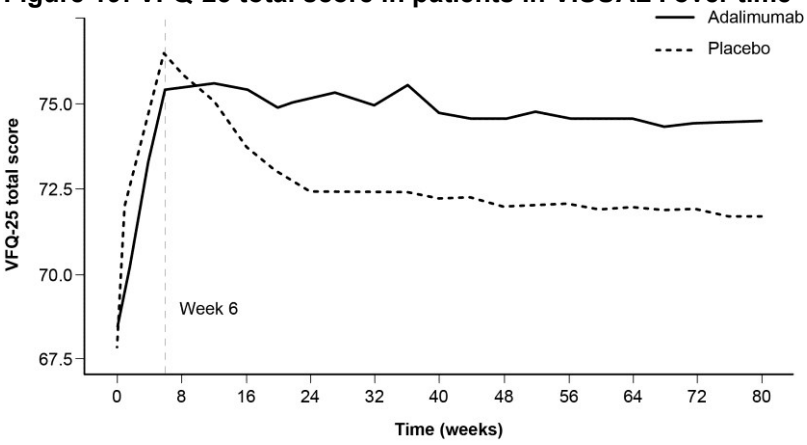
ADA-treated patients had a statistically significant and clinically meaningful improvement (Δ = 4.2, p=0.01) relative to placebo in terms of change in VFQ-25 total score.

Data presented at ARVO 2015 revealed the results of a repeated measures analysis using generalized estimating equations methodology to investigate the temporal effects of ADA and PBO on VFQ-25[47]. Post-steroid taper, the average decline in the PBO arm was 0.18/month and < 0.01/month with ADA. Overall the mean difference, between ADA and PBO was estimated to be 3.07, p<0.001.

Table 14: Ranked VRQOL secondary end-points in VISUAL I[21].

		PBO (n=102)	ADA (n=101)	Difference (95% CI)	p value
6. Change in VFQ-25 composite score	Baseline	77.18 (17.17)	75.79 (18.26)	4.20 (1.02–7.38)	0.010
	Change	-5.50 (11.97)	-1.30 (10.98)		
7. Change in VFQ-25 distance vision subscale	Baseline	77.33 (20.43)	75.91 (22.25)	1.86 (-2.03–5.75)	0.346
	Change	-5.64 (14.65)	-3.77 (13.41)		
8. Change in VFQ-25 near vision subscale	Baseline	76.92 (19.46)	74.79 (23.53)	5.12 (0.34–9.90)	0.036
	Change	-8.09 (17.75)	-2.97 (16.78)		
9. Change in VFQ-25 ocular pain subscale	Baseline	84.07 (16.42)	83.66 (18.26	10.02 (4.86–15.19)	<0.001
	Change	-12.62 (21.44)	-2.6 (15.34)		

Figure 19: VFQ-25 total score in patients in VISUAL I over time[21].

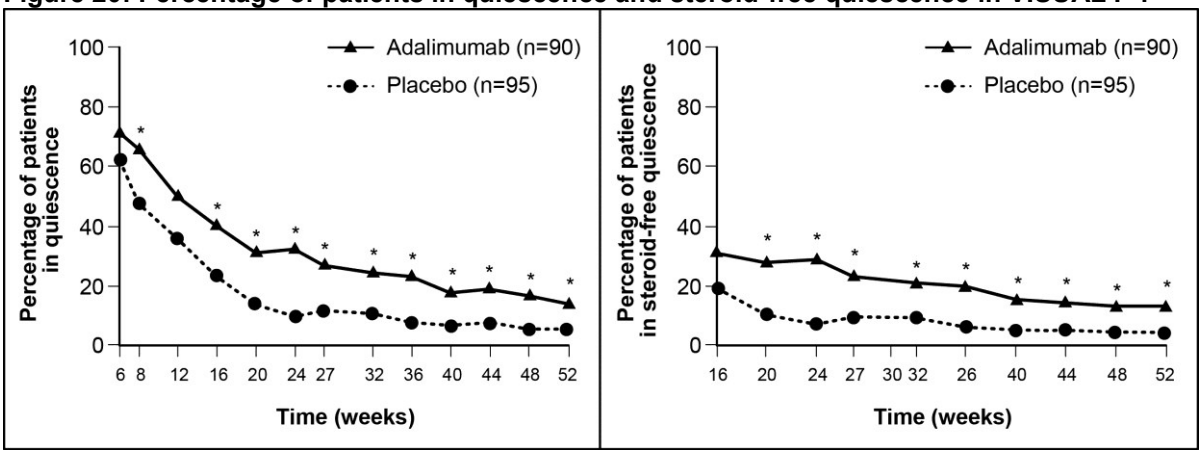


3.4.4 Disease quiescence

Quiescence, as a very stringent outcome measure for inflammation control, was reported in a poster presented at EULAR in 2016[46].

The proportions of patients in quiescence and steroid-free quiescence were significantly higher in the ADA group compared to PBO at all scheduled visits with the exception of week 6 and week 12 for VISUAL I, see Figure 20.

Figure 20: Percentage of patients in quiescence and steroid-free quiescence in VISUAL I[46].



*=p<0.05

3.4.5 Patient reported outcomes

Other efficacy end-points – HRQOL (using the EQ-5D), anxiety and depression (using the HADS), mental health (subscale of the VFQ-25), work productivity (using the WPAI) and level of HRU – were also assessed in the VISUAL I trial[21].

- EQ-5D assessment of HRQOL found higher values for the ADA group compared to the PBO group. Statistical significance in favour of ADA was found in EQ-5D predicted value when looking at change from best state achieved prior to week 6 to final (or early termination) visit (mean difference: 0.04, p=0.044).

- No significant differences were seen between ADA and PBO groups in HADS scores for either anxiety or depression.

- There was a significant improvement in mental health with ADA as measured by the mental health subscale of the VFQ-25 (mean difference 5.25, p=0.033).

- A statistically larger reduction in work time missed was recorded by WPAI in the ADA group compared to the placebo group (mean difference -10.61 days, p=0.011). No other significant differences were recorded between the two groups.

- No significant differences were seen in HRU between the ADA and PBO groups.

3.5 VISUAL II: efficacy results

- In VISUAL II, the median time to treatment failure was not reached in the ADA group (>18 months) and was 8.3 months in the PBO group[22].
- Patients receiving ADA were significantly (p=0.004) less likely to experience treatment failure than the PBO group: HR was 0.57 (95% CI: 0.39–0.84)[22].
- The visual acuity component of the primary end-point showed significant benefit with ADA over PBO. Numerical benefit was seen in the other components[22].
- The use of permitted concomitant immunosuppressants did not significantly alter the time to treatment failure in either the ADA or PBO group[20].
- The secondary end-points demonstrated numerical benefit in visual acuity, inflammation, macular oedema and VRQOL with ADA compared with PBO[22].
- The proportions of patients in quiescence and steroid-free quiescence were significantly higher in the ADA group compared to PBO at all scheduled visits with the exception of week 16[20].
- No significant differences were seen in the PRO assessed in VISUAL II[20].

3.5.1 Primary end-point

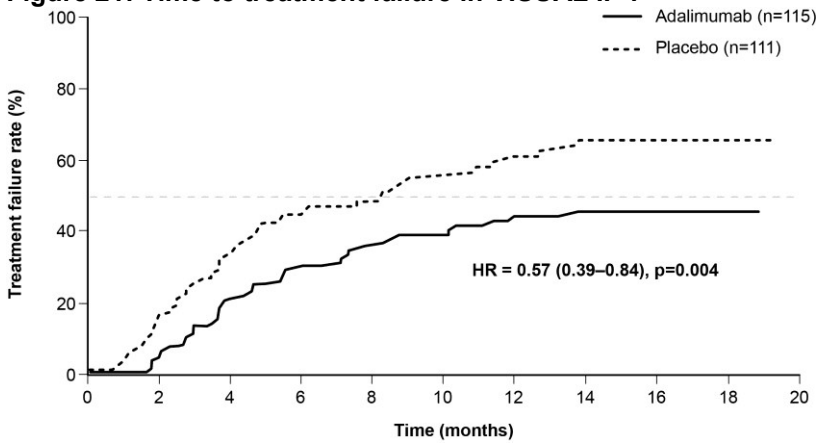
VISUAL II was published in *The Lancet* (online first) on August 16th 2016. Data on the primary end-point has also been presented at international conferences. We have used the published paper[22] and data presented at the American College of Rheumatology (ACR) in 2015[43] to inform this section, together with the CSR[20].

The primary end-point was a composite made up of measures of inflammation and visual acuity (inflammatory, chorioretinal and/or retinal vascular lesions, AC cell grade, VH grade and visual acuity).

In VISUAL II the primary end-point was time to treatment failure defined as presence of at least one of the criteria on or after week 2.

The median time to treatment failure was not reached in the ADA group (>18 months) and was 8.3 months in the PBO group. With a HR of 0.57 (95% CI: 0.39–0.84), patients receiving ADA were significantly (p=0.004) less likely to experience treatment failure than the PBO group.

Figure 21: Time to treatment failure in VISUAL II[22].



Analysis of time to treatment failure once stratified for the use of permitted immunosuppressant therapies showed no significant difference in HR compared to the primary analysis (Table 15), showing that the use of permitted concomitant immunosuppressants did not significantly alter the time to treatment failure in either the ADA or PBO group.

Table 15: Time to treatment failure at or after week 6, adjusted for immunosuppressant use at baseline in VISUAL II[21].

	Treatment failure n (%)	Median time to treatment failure	HR	p value
PBO (n=111)	61 (55.0%)	8.3	0.58 (0.39,0.85)	0.005
ADA (n=115)	45 (39.1%)	Not reached		

The components of the composite end-point were also assessed, significant benefit was seen in the ADA arm in terms of visual acuity, HR=0.33 95% CI: 0.16–0.7, p=0.002 (Figure 25) and numerical benefit was seen in the ADA arm in inflammation (VH grade, AC cell grade and development of new inflammatory lesions), see Figure 22 to Figure 24.

Figure 22: Treatment failure due to development of new inflammatory lesions in VISUAL II[22].

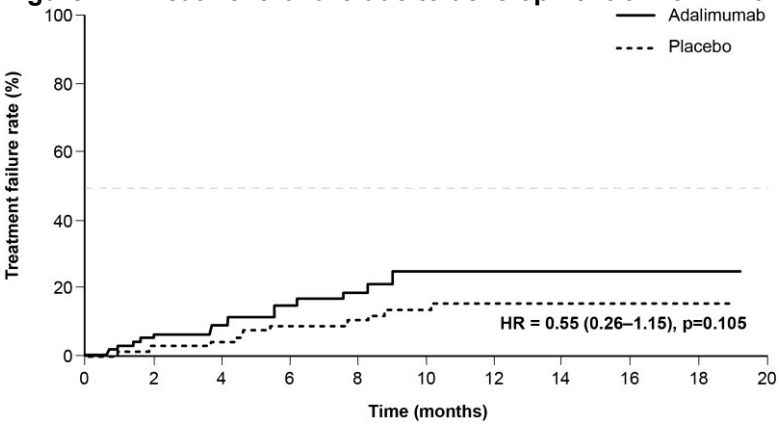


Figure 23: Treatment failure due to worsening of AC cell grade in VISUAL II[22].

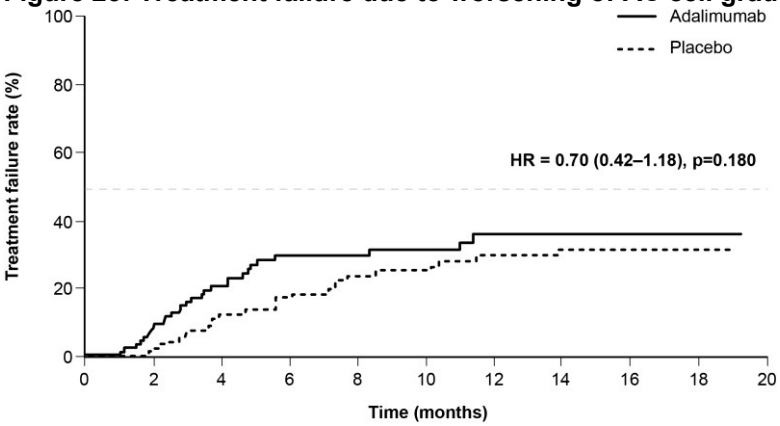


Figure 24: Treatment failure due to worsening of VH grade in VISUAL II[22].

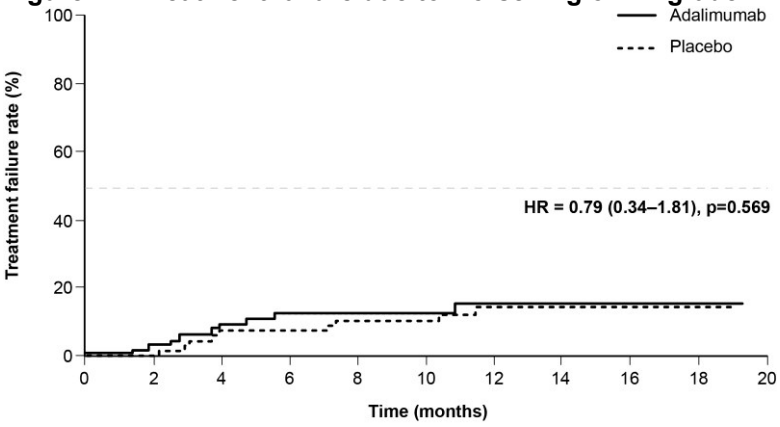
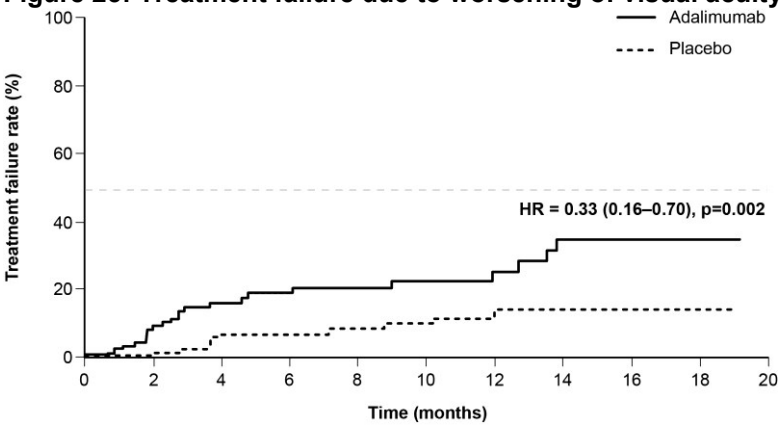


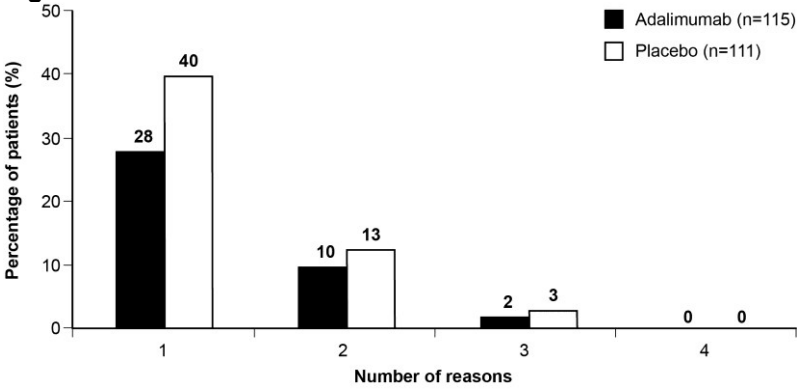
Figure 25: Treatment failure due to worsening of visual acuity grade in VISUAL II[22].



The number of reasons met for treatment failure was higher for the placebo group compared with the ADA group, see Figure 26.

Treatment failure was driven by vision loss; the reason for treatment failure which demonstrated the largest difference between treatment groups was visual acuity (21% and 9% for PBO and ADA groups, respectively)[22].

Figure 26: Number of criteria met for treatment failure in ADA and PBO arms in VISUAL II[22].



3.5.2 Secondary end-points: clinical

The clinical secondary end-points are shown in Table 12. Overall, no statistically significant differences were observed between the treatment groups for any of the ranked secondary efficacy variables. Results were numerically in favour of ADA compared with patients receiving PBO.

Table 16: Ranked clinical secondary end-points in VISUAL II[22].

Ranked secondary end-points*	PBO (n=107)		ADA (n=110)		
	n	Mean	n	Mean	p value
1. Change in AC cell grade					
Left eye	110	0.57	115	0.41	
Right eye	110	0.53	115	0.40	
Difference, mean (95% CI)	-0.14 (-0.37 to 0.08)				0.218†
2. Change in VH grade					
Left eye	110	0.33	115	0.16	
Right eye	110	0.27	115	0.18	
Difference, mean (95% CI)	-0.13 (-0.28 to 0.01)				<0.070†
3. Change in BCVA, logMAR					
Left eye	110	0.06	115	0.01	
Right eye	110	0.02	115	-0.01	
Difference, mean (95% CI)	-0.04 (-0.08 to 0.01)				0.096†
4. Time to evidence of CMO on or after week 2 (patients without CMO at baseline) [Pre-specified analysis]					
Median	96	NE	90	NE	
HR (95%CI)	0.75 (0.34 to 1.69)				0.491‡
5. Percentage change in CRT [Pre-specified analysis]					
Left eye	107	6.4	114	4.5	
Right eye	107	7.7	113	5.4	
Difference, mean (95% CI)	-2.3 (-8.5 to 3.8)				0.451‡

†p value from analysis of variance with treatment and type of OCT machine as a factor and adjusted for clustered observations. ‡HR of ADA versus PBO from proportional hazards regression with treatment as factor.
*Unless otherwise noted, data reflect change from baseline to the final or early termination visit.

3.5.3 Secondary end-points: VRQOL

Treatment with ADA did not correspond to a statistically significant improvement relative to PBO for the VFQ-25 total score. However, a statistically significant improvement was seen for two of the subdomains, general vision (6.46, 95% CI: 2.28–10.65) and mental health (5.55, 95% CI: 0.79–10.30). This difference was subject to the minimal clinically important difference of one standard error of measurement as previously defined in literature.

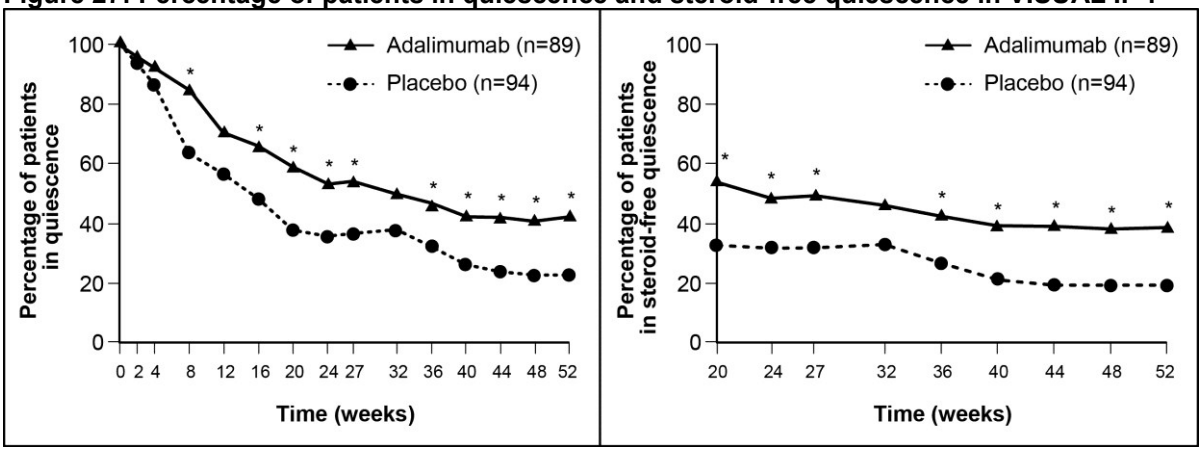
Treatment with ADA did not correspond to a statistically significant improvement relative to PBO for the other ranked VFQ-25 scores (distance vision, near vision and ocular pain).

3.5.4 Disease quiescence

Quiescence was reported in a poster presented at EULAR in 2016[46].

The proportions of patients in quiescence and steroid-free quiescence were significantly higher in the ADA group compared to PBO at all scheduled visits with the exception of week 16 for VISUAL II, see Figure 27.

Figure 27: Percentage of patients in quiescence and steroid-free quiescence in VISUAL II[46].



*=p<0.05

3.5.5 Patient reported outcomes

Other efficacy end-points – HRQOL (using the EQ-5D), anxiety and depression (using the HADS), work productivity (using the WPAI) and level of HRU – were also assessed in the VISUAL II trial[20]. No significant differences were seen in the PRO assessed in VISUAL II.

3.6 Non-RCT clinical studies

Data from non-RCT studies is not included within this submission, since robust RCT data is available from VISUAL I and VISUAL II.

3.7 Audit data

The Clinical Commissioning Policy for anti-TNF treatment options for adult patients with severe refractory uveitis contains details of a retrospective audit of data from a multicentre ocular inflammation biologics registry which captured routine clinical data in uveitis within the UK[48]. Patients >18 years who received either ADA (40 mg/^{2} per week) or infliximab (3-5 mg/kg every 2 weeks) were included in the audit. All patients (n=41) on biologics showed clinical remission after a mean (± SD) follow-up of 1.36 (± 0.88) person years. More patients had an improvement in visual acuity than had worsening of visual acuity (48.8% versus 17.1%). Steroid dose was reduced to <10 mg prednisone in the majority of patients (88.9%) and almost half of patients (45.2%) stopped steroid use altogether. There was also a reduction in the use of immunosuppressants; 83.33% of patients on biologics had a reduction in the number and/or use of immunosuppressants.

3.8 Studies unpublished at the time of writing

The open label follow-on study, VISUAL III, is currently unpublished; interim data will be presented in August 2016 at the International Uveitis Study Group in Dublin[23].

Patients that discontinued VISUAL I or VISUAL II due to treatment failure had active disease at VISUAL III entry. Efficacy end-points included new inflammatory lesions, AC cell and VH grades from study entry (week-0) through week-54 (controlled uveitis) and week-78 (active uveitis). Corticosteroid daily dose was measured over time.

ITT analyses included 243 (active) and 128 (controlled) uveitis patients at study entry. The results reflect benefit with ADA although there is no comparator. At week 54, no new inflammatory lesions relative to baseline, AC cell and VH grades of ≤0.5+ were observed in 98.5%, 98.5% and 92.6% of controlled uveitis patients, respectively. At week 78, no new inflammatory lesions relative to week-8, AC cell and VH grades of ≤0.5+ were observed in 96.3%, 91.0% and 87.8% of active uveitis patients, respectively. Mean systemic corticosteroid daily dose decreased by 71% for patients with active uveitis and remained stable for controlled patients.

3.9 VISUAL I and II: safety results

- AEs were broadly similar between the ADA and PBO groups. The safety profile was consistent with the known safety profile of ADA across approved indications and the uveitis indication. No new safety signals were identified in either study[22,24].
- There was one death in VISUAL I and one in VISUAL II, both were in patients receiving ADA, however, the deaths were not considered to be related to ADA treatment[20,21].
- The most frequently reported AE in VISUAL I and VISUAL II were nasopharyngitis, fatigue and headache. Most events occurred in <10% of patients and rates were comparable between ADA and PBO[20-22].

3.9.1 Overall safety

AEs were broadly similar between the ADA and PBO groups. The safety profile was consistent with the known safety profile of ADA across approved indications and the uveitis indication. No new safety signals were identified in either study[22,24].

An analysis of patient-years provides a more appropriate measure of AE reporting than absolute counts in this trial design, as a higher number of patients failed in the PBO arm compared with the ADA arm (Table 17).

Data is also presented as number and percentage of patients experiencing the event (Table 18). In both studies, there was no significant difference in AE, serious AE (SAE) or in AE leading to discontinuation between ADA and PBO[20,21]

Table 17: Summary of treatment-emergent AE across the randomised trials – events per 100 patient years[22,24].

	VISUAL I		VISUAL II	
	PBO n=112 PYs=44.3 Events (E/100PY)	**ADA n=111 PYs=62.4 Events (E/100PY)**	**PBO n=114 PYs=71.0 Events (E/100PY)**	**ADA n=115 PYs=94.5 Events (E/100PY)**
Any AE	430 (972)	657(1052)	642 (905)	831 (879)
Injection site reactions	7 (15.8)	28 (44.9)	16 (22.6)	36 (38.1)
Serious AE (SAE)	6 (13.6)	18 (28.8)	10 (14.1)	13 (13.8)
AE leading to discontinuation	5 (11.3)	13 (20.8)	7 (9.9)	11 (11.6)
Serious infections	3 (6.8)	5 (8)	2 (2.8)	3 (3.2)
Malignancy	0	2 (3.2)	0	1 (1.1)
Any active TB	0	1 (1.6)	0	0
Any latent TB	0	1 (1.6)	1 (1.4)	3 (3.2)
Any demyelinating disease	0	1 (1.6)	0	0
Death	0	1 (1.6)	0	1 (1.1)

Table 18: Summary of treatment-emergent AE across the randomised trials, n (%)[20,21].

	VISUAL I		VISUAL II	
	PBO n=112 n (%)	**ADA n=111 n (%)**	**PBO n=114 n (%)**	**ADA n=115 n (%)**
Any AE	88 (78.6%)	94 (84.7%)	96 (84.2%)	105 (91.3%)
Injection site reactions	7 (6.3%)	7 (6.3%)	16 (22.6)	36 (38.1)
SAE	5 (4.5%)	15 (13.5%)	9 (7.9%)	7 (6.1%)
AE leading to discontinuation	4 (3.6%)	11 (9.9%)	7 (6.1%)	10 (8.7%)
Serious infections	2 (1.8%)	5 (4.5%)	2 (1.8%)	2 (1.7%)
Malignancy	0	2 (1.8%)	0	1 (0.9%)
Any active TB	0	1 (0.9%)	0	0
Any latent TB	0	1 (0.9%)	1 (0.9%)	3 (2.6%)
Any demyelinating disease	0	1 (0.9%)	0	0
Death	0	1 (0.9%)	0	1 (0.9%)

There was one death in VISUAL I. An 80-year-old white female randomised to the ADA group, died on Day 37 (3 days post-treatment) as a result of renal failure. The investigator considered this event not related to ADA and provided an alternate aetiology of end stage renal disease[21].

There was one death in VISUAL II. A 62-year-old white male randomised to the ADA group, died on Day 54 (18 days after last dose) as a result of aortic dissection and cardiac tamponade. The investigator considered these events as not related to ADA and provided an alternate aetiology of abdominal aortic aneurysm.

3.9.2 Most frequently reported AE

The most frequently reported AE in VISUAL I and VISUAL II are shown in Table 19. It can be seen from the table that the most commonly reported events were nasopharyngitis, fatigue and headache. Most events occurred in <10% of patients and rates were comparable between ADA and PBO.

Table 19: Summary of AEs reported by ≥5% of patients in the ADA arm in VISUAL I and experienced by at least two patients in VISUAL II[20,21].

	VISUAL I		VISUAL II	
	ADA n=112 n (%)	PBO n=111 n (%)	ADA n=114 n (%)	PBO n=115 n (%)
Any treatment emergent AE	88 (78.6%)	94 (84.7%)	52 (45.6%)	64 (55.7%)
Nasopharyngitis	8 (7.1%)	21 (18.9%)	6 (5.3%)	6 (5.2%)
Fatigue	7 (6.3%)	12 (10.8%)	5 (4.4%)	3 (2.6%)
Headache	15 (13.4%)	12 (10.8%)	6 (5.3%)	4 (3.5%)
Uveitis*	8 (7.1%)	11 (9.9%)	3 (2.6%)	2 (1.7%)
Arthralgia	11 (9.8%)	10 (9.0%)	1 (0.9%)	3 (2.6%)
Back pain	2 (1.8%)	9 (8.1%)		
Eye pain	2 (1.8%)	9 (8.1%)		
Vision blurred	2 (1.8%)	8 (7.2%)		
Bronchitis	4 (3.6%)	7 (6.3%)	3 (2.6%)	0
Cough	4 (3.6%)	7 (6.3%)		
Hyperhidrosis	3 (2.7%)	7 (6.3%)		
Muscle spasms	4 (3.6%)	7 (6.3%)		
Urinary tract infection	0	7 (6.3%)	4 (3.5%)	4 (3.5%)
Nausea	7 (6.3%)	6 (5.4%)	3 (2.6%)	2 (1.7%)
Paraesthesia	0	6 (5.4%)	1 (0.9%)	3 (2.6%)
Alanine aminotransferase increased			0	6 (5.2%)
Aspartate aminotransferase increased			0	5 (4.3%)
Pain in extremity			1 (0.9%)	4 (3.5%)
Upper respiratory tract infection			1 (0.9%)	4 (3.5%)
Dermatitis			1 (0.9%)	3 (2.6%)
Eczema			0	3 (2.6%)
Insomnia			0	3 (2.6%)
Influenza			3 (2.6%)	2 (1.7%)
* Worsening of a pre-existing condition or illness was considered an AE.				

3.9.3 Long-term safety during open-label treatment

The open label follow-on study, VISUAL III, is currently unpublished, interim data will be presented in August 2016 at the International Uveitis Study Group in Dublin[23].

AE rates (577 AE/100PY and 19.6 SAE/100PY) in VISUAL III were comparable to the VISUAL I and VISUAL II trials.

3.10 Clinical interpretation of the evidence

- ADA demonstrated a positive effect versus PBO in two different populations: patients with active disease despite corticosteroid use for at least 2 weeks (oral prednisone 10-60 mg/day or oral corticosteroid equivalent) and those with controlled disease requiring corticosteroid use to maintain inactivity (oral prednisone >10 mg/day to ≤35 mg/day or oral corticosteroid equivalent)[21,22].
- The composite primary end-point of time to treatment failure, made up of measures of inflammation and visual acuity (retinal vascular lesions, AC cell grade, VH grade and visual acuity) was significantly extended by the use of ADA[21,22].
- The secondary end-points demonstrated significant benefit in visual acuity, inflammation, macular oedema and VRQOL with ADA compared with PBO in VISUAL I. However, in VISUAL II, although benefit was seen numerically with ADA for most measures, the benefit did not reach significance, which might be due to the differences in disease activity at baseline between the two studies – controlled disease rather than active disease [21,22].
- ADA shows early and sustained activity: the Kaplan-Meier curves separated early in the study –

at the first measurable time-point in both studies (week 6 in VISUAL I and week 2 in VISUAL II). Benefit in the ADA arm was sustained for 5.6 months in VISUAL I and for >18 months in VISUAL II without the use of steroids[21,22].

- Maintenance of visual acuity: visual acuity was maintained for significantly longer with ADA compared with PBO in both VISUAL studies. The risk of treatment failure based on visual acuity only was reduced in patients receiving ADA by 44% in VISUAL I and by 67% in VISUAL II compared with PBO. The significant benefit seen with ADA over PBO in the pre-specified *post hoc* analyses in patients without macular hole and/or retinal detachment in VISUAL I suggests that ADA slows the development of macular oedema in patients with active disease[21].
- ADA has a steroid sparing effect, in both VISUAL studies patients were able to stop using corticosteroids until treatment failure[20,21].
- ADA was well tolerated, there were low discontinuation rates and no significant difference in AE rates between ADA and PBO in either study[21,22].

3.10.1 Benefits of treatment

The VISUAL study programme is the first successful programme where the treatment effect of the study drug (ADA) was sustained for the entire study duration in two separate randomised controlled trials involving different uveitis patient populations[46].

ADA demonstrated a positive effect versus PBO in two different populations:

- Patients with non-infectious, intermediate, posterior and pan uveitis with active disease despite corticosteroid use for at least 2 weeks (oral prednisone 10-60 mg/day or oral corticosteroid equivalent); the VISUAL I population.

- Patients with non-infectious, intermediate, posterior and pan uveitis with controlled disease requiring corticosteroid use to maintain inactivity (oral prednisone >10 mg/day or oral corticosteroid equivalent); the VISUAL II population.

The composite primary end-point of time to treatment failure, made up of measures of inflammation and visual acuity (retinal vascular lesions, AC cell grade, VH grade and visual acuity) was significantly extended by the use of ADA.

In VISUAL I, the risk of treatment failure was statistically significantly reduced by 50% for patients in the ADA group compared with PBO (HR: 0.5, 95% CI: 0.36–0.70; p<0.001 from log rank test). Patients in the ADA group took longer to experience treatment failure than those receiving PBO (5.6 months versus 3 months). Each of the individual components of the primary end-point was significantly improved in the ADA group versus PBO[24].

In VISUAL II, the risk of treatment failure was statistically significantly reduced by 43% for patients in the ADA group compared with PBO (HR: 0.57, 95% CI: 0.39–0.84; p=0.004). Patients in the ADA group took longer to experience treatment failure than those receiving PBO (>18 months versus 8.3 months). Significant benefit was seen in the ADA arm in terms of visual acuity, HR=0.33 95% CI: 0.16–0.7, p=0.002 and numerical benefit was seen in the ADA arm in measures of inflammation[22].

Sensitivity analysis adjusting the HR for baseline immunosuppressant usage (ITT) demonstrated no influence of concomitant immunosuppressant use on the effect of ADA in both studies.

The composite end-point used in the VISUAL studies reflects both inflammation and visual function. Two elements of the composite end-point (AC cell grade and VH grade) are measures of both inflammation and visual function. AC cell grade provides a measure of inflammation in the AC, where an increase in the number of AC cells may reduce visual function. VH grade, provides a measure of inflammation in the vitreous, where a higher VH grade may lead to increasingly blurred vision. Retinal vascular lesions are a measure of inflammation and visual acuity is a measure of visual function.

[redacted]

[redacted]

The four criteria which make up the composite end-point reflect the real world complexity of the disease using clinically meaningful flare measures. Indeed data from a study which assessed the relationship between clinician-assessed treatment failure in VISUAL I and VISUAL II and patient reported changes in VRQOL using VFQ-25 found that in both studies treatment failure, as defined in the clinical trials, was associated with clinically meaningful decreases in VFQ-25. Thus supporting treatment failure as a relevant outcome from the patients' perspective[45].

The secondary end-points demonstrated significant benefit in visual acuity, inflammation, macular oedema and VRQOL with ADA compared with PBO in VISUAL I. However, in VISUAL II, although benefit was seen numerically with ADA for most measures, the benefit did not reach significance. This might be due to the differences in disease activity at baseline between the two studies (controlled disease rather than active disease). Data suggests that more patients have controlled disease than have active disease[49,50]. A study assessing the use of methotrexate in patients with non-infectious ocular inflammation found that steroid sparing (prednisone ≤10 mg/day) was only achieved in 41.3% of patients with intermediate uveitis, 20.7% with posterior uveitis and 37.3% with pan uveitis at 6 months[49].

The key benefits of ADA in non-infectious, intermediate, posterior and pan uveitis are listed below:

- Early and sustained activity: the Kaplan-Meier curves separated early in the study – at the first measurable time-point in both studies (week 6 in VISUAL I and week 2 in VISUAL II). Benefit in the ADA arm was sustained for 5.6 months in VISUAL I and for >18 months in VISUAL II without the use of steroids.
- Maintenance of visual acuity: visual acuity was maintained for significantly longer with ADA compared with PBO in both VISUAL studies. The risk of treatment failure based on visual acuity only was reduced in patients receiving ADA by 44% in VISUAL I and by 67% in VISUAL II compared with PBO.
- Reduction in inflammation: measures of inflammation were significantly reduced in VISUAL I and numerically in VISUAL II.
- Reduction in macular oedema: macular oedema is a major cause of vision loss in people with uveitis[1]. The significant benefit seen with ADA over PBO in the pre-specified *post hoc* analyses in patients without macular hole and/or retinal detachment in VISUAL I suggests that ADA may slow the development of macular oedema. There was no significant difference in macular oedema outcomes in VISUAL II.
- Steroid sparing effect: prolonged steroid use is not recommended and corticosteroids need to be used with care because of the associated complications, related to the dose and duration of treatment, which include ocular complications (raised IOP and formation of cataract), osteoporosis, diabetes, susceptibility to infection, adrenal suppression and changes in mood and behaviour[1,15]. In both VISUAL studies, patients were able to stop using corticosteroids until treatment failure. The proportions of patients in quiescence and steroid-free quiescence were significantly higher in the ADA group compared to PBO in both studies. In a *post-hoc* analysis in the placebo arm of VISUAL I (patients with active uveitis on oral prednisone, starting on 60 mg/day), corticosteroid-related AEs incidence rate ratio (IRR) before and after the end of the steroid taper period was 12 times higher compared to the other AEs that were not corticosteroid related (corticosteroid related IRR=12.6, p<0.01; corticosteroid not related IRR = 1.17, p<0.36)[51,52]. [redacted]
- Benefits in vision-related functioning: loss of sight has a significant impact on patients' QOL and the VISUAL studies both assessed VRQOL using the VFQ-25 scale. Significant benefit was seen in the total (composite) score and in near vision, general vision and ocular pain in VISUAL I.
- Benefits in HRQOL and in work productivity: there was a significant improvement in HRQOL (as measured by EQ-5D), mental health (as measured by the mental health subscale of the VFQ-25)

and a reduction in work time lost as measured on the WPAI in patients receiving ADA compared to those receiving PBO in VISUAL I. There was no significant difference in PROs in VISUAL II.

Discontinuations were low in both VISUAL studies, <10% of patients discontinued due to AE or lack of efficacy and there was no significant difference in discontinuations between ADA and PBO across either study.

AEs were similar between the ADA and PBO groups. The safety profile was consistent with the known safety profile of ADA across approved indications and the uveitis indication. No new safety signals were identified in either study and no deaths were attributed to the use of ADA[20,22,24].

3.10.2 Limitations of the study programme

The VISUAL study programme compared ADA with PBO, rather than an active comparator. This reflects the treatment sequence for uveitis – first-line corticosteroids, second-line systemic immunosuppressive therapies and third-line biologics. In practice, most patients will require combination treatment with corticosteroids plus one or more systemic immunosuppressive treatments and potentially biologics. Guidelines suggest that biologics have a role in treating sight-threatening uveitis refractory to conventional immunosuppression. They may be used as steroid sparing agents or where other immunosuppressive agents are poorly tolerated as well as when ocular inflammation remains uncontrolled. There is no active licensed comparator for ADA in the treatment sequence above. It should be noted that even among immunosuppressive treatments, only cyclosporine is licensed for uveitis; all other immunosuppressants are used outside their licensed indications.

The scope for this submission recommends comparators should include corticosteroids (drops, implants, systemic), systemic immunosuppressive treatments and best supportive care. Given that biologics are the last line of treatment, it is not appropriate to compare ADA with earlier lines of therapy with the most appropriate comparator being best supportive care.

Indeed, the VISUAL studies were designed to assess the use of ADA in patients with active (VISUAL I) and controlled (VISUAL II) disease without the use of corticosteroids. As part of the study design corticosteroids were tapered to discontinuation. In VISUAL I, there was a mandatory 60 mg/day burst of prednisone at week 0 tapered to discontinuation at week 15 and in VISUAL II prednisone 10-35 mg/day was tapered to discontinuation at week 19.

The positive outcome of the VISUAL studies resulted in a licence for ADA. ADA is licensed for the treatment of non-infectious intermediate, posterior and pan uveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing or in whom corticosteroid treatment is inappropriate[17], therefore, corticosteroids are not a appropriate comparator for ADA.

In the VISUAL studies for ethical reasons (PBO arm), patients were able to continue taking systemic immunosuppressants: methotrexate, cyclosporine, mycophenolate mofetil or an equivalent drug to mycophenolate mofetil (e.g. mycophenolic acid), AZA or tacrolimus. Indeed, around one-half (47%) of patients were taking concomitant immunosuppressant in VISUAL I and around one-third (30%) in VISUAL II. However, in clinical practice systemic immunosuppressants would be expected to be used as a second line treatment option and therefore systemic immunosuppressants are not an appropriate comparator for ADA.

The results of the VISUAL studies demonstrate that ADA has significant benefit over PBO. Since biologics will be used as the final line of treatment and there is no other licensed biologic or other licensed agent with which to compare ADA in this setting, best supportive care represented by the PBO arm of the VISUAL studies is the most appropriate comparator to ADA.

3.11 Meta-analysis

No formal meta-analysis was conducted as part of this submission.

4 Implications for the NHS

Uveitis can result in a wide range of complications for people with the disease, their carers, the NHS and society in general. The economic impact of this disease includes:

- Direct costs to the NHS and associated healthcare support services.
- Indirect costs to the economy, including the effects of blindness and lost productivity.
- The personal impact of uveitis and subsequent complications for people with uveitis and their families.

Patients with uveitis are at a significant risk of developing substantial and sometimes permanent loss of vision. Uveitis and its associated complications are the fifth most common cause of vision loss in the developed world, accounting for 10% of all cases of total blindness[2]. The total cost of blindness in the UK was estimated at £22.0 billion in 2008. Direct health care system costs amounted to £2.14 billion and indirect costs amounted to £4.34 billion. In addition, the loss of healthy life and the loss of life due to premature death associated with partial sight and blindness also impose a cost on society through a reduction in the stock of health capital. This reduction was estimated at £15.51 billion in 2008[54].

4.1 Budget impact model

- For the purpose of this budget impact calculation we have only included drug acquisition costs to the NHS. The annual cost per patient of treating non-infectious intermediate, posterior and pan uveitis with ADA is estimated to be £9,507.78 in Year 1 and £9,155.64 in subsequent years.
- The total number of patients expected to be treated with ADA would be 175 in Year 1 rising to 556 by Year 5.
- The total budget impact of ADA introduction is expected to be £1,551,011 in Year 1 rising to £4,766,996 in year 5.

The total annual budget impact estimates presented below are based on prevalent patients with non-infectious intermediate, posterior and pan uveitis in Year 1 and incident plus prevalent cases of patients with non-infectious intermediate, posterior and pan uveitis in subsequent years.

Estimates of the population-wide incidence and prevalence of uveitis vary. Based on data from the EQUINOX study conducted by AbbVie[14] the annual incidence of uveitis in people aged over 18 years has been estimated to be around 0.0027% equivalent to around 1,174 people over the age of 18 years per year in England. The population prevalence of uveitis in the UK adult population has been estimated to be 0.094% (which equates to around 40,856 people over the age of 18 years in England). Of these uveitis cases the majority will be anterior uveitis with only 13.2% expected to be classified as non-infectious intermediate, posterior and pan uveitis.

Given that not all patients would be under physician care and receiving drug treatment, AbbVie has assumed that 95% of patients would currently be under the care of a physician and of these a further 95% would actually be receiving pharmacological treatment. In the UK it is estimated that 40% of patients with non-infectious intermediate, posterior and pan uveitis are either not appropriate for/had an inadequate response to/are dependent upon systemic corticosteroids and could be candidates for biologics. However in clinical practice it is likely that further combinations would be tried before prescribing biologics (including combining conventional second-line agents and using suboptimally high doses of corticosteroids). Therefore, the biologic penetration is expected to be low at 10% in Year 1 rising to 30% in Year 5 once physicians become more familiar with the use of ADA. Given that no other biologic treatments are licensed for uveitis in the UK, AbbVie has assumed that ADA will have 90% of the market share. Therefore, the total number of patients AbbVie anticipates to be treated with ADA is 175 in Year 1 rising to 556 in Year 5 (Table 20).

Table 20: Estimate of total number of patients expected to be treated with ADA in England in Years 1 to 5 after introduction

	2016	2017	2018	2019	2020
Projected population England [55]	55,218,700	55,640,400	56,061,500	56,466,300	56,862,300
Proportion of all aged 18 & over [56]	*78.71%*	*78.71%*	*78.71%*	*78.71%*	*78.71%*
Number of people	43,463,593	43,795,521	44,126,976	44,445,601	44,757,299
Diagnosed prevalence of uveitis[14]	*0.094%*	*0.094%*	*0.094%*	*0.094%*	*0.094%*
Incidence[14]	-	*0.0027%*	*0.0027%*	*0.0027%*	*0.0027%*
Total patients with uveitis	40,856	42,350	42,671	42,979	43,280
Diagnosed % non-infectious intermediate, posterior and pan uveitis[14]	*13.2%*	*13.2%*	*13.2%*	*13.2%*	*13.2%*
Total patients diagnosed with non-infectious intermediate, posterior and pan uveitis	5,389	5,587	5,629	5,670	5,709
% under physician care [57]	*95.0%*	*95.0%*	*95.0%*	*95.0%*	*95.0%*
Total patients under physician care	5,120	5,307	5,347	5,386	5,424
% drug treated [57]	*95.0%*	*95.0%*	*95.0%*	*95.0%*	*95.0%*
Total patients drug treated	4,864	5,042	5,080	5,117	5,153
% not appropriate for/had an inadequate response to/are dependent upon systemic corticosteroids [57]	*40.0%*	*40.0%*	*40.0%*	*40.0%*	*40.0%*
Total patients	1,946	2,017	2,032	2,047	2,061
% biologic treated [57]	*10.0%*	*15.0%*	*20.0%*	*25.0%*	*30.0%*
Biologic treated uveitis patients	195	303	406	512	618
ADA peak share of biologic treated patients [57]	*90.0%*	*90.0%*	*90.0%*	*90.0%*	*90.0%*
ADA-treated patients	**175**	**272**	**366**	**461**	**556**

ADA is licensed for the treatment of non-infectious intermediate, posterior and pan uveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing or in whom corticosteroid treatment is inappropriate[17]. As a last line of treatment and with no other pharmacological treatment option available the only alternative option would best supportive care (BSC). However in clinical practice upon failure of systemic immunosuppressants it's highly likely that physician would be still prescribing oral corticosteroids in order to control uveitis flares; therefore, in the budget impact it is assumed that patients on BSC would be receiving a dose of 10 mg of prednisone per day.

The annual cost per patient of treating uveitis with ADA is estimated to be £9,508.78 in Year 1 and £9,155.64 in subsequent years. This represents the drug acquisition cost. No administration costs or VAT have been included as it is assumed that ADA will be administered by the patient outside of the hospital setting. The annual cost per patient of treating uveitis with oral prednisone (10 mg per day) is £650.15.

For the purpose of this budget impact calculation only drug acquisition costs to the NHS have been included. In order to estimate the annual budget impact to the NHS with the introduction of ADA the annual cost per patient of each treatment option (ADA and BSC) in Year 1 has been multiplied by the total number of patients eligible for each treatment option in each of the years considered in the

analysis. The total budget impact for ADA is calculated as the difference between the total costs of treatment if ADA is adopted minus the total cost of treatment if patients continued to receive BSC.

The total annual treatment costs with ADA introduction are presented in Table 21.

Table 21: Total annual treatment costs with ADA introduction.

	Year 1	Year 2	Year 3	Year 4	Year 5
Uveitis patients treated with a biologic	195	303	406	512	618
ADA market share	90%	90%	90%	90%	90%
Patients receiving ADA	175	272	366	461	556
Total cost of patients receiving ADA	£1,664,854	£2,526,969	£3,381,754	£4,249,624	£5,128,794

The total annual treatment costs without the introduction of ADA are presented in Table 22.

Table 22: Total annual treatment costs without the introduction of ADA.

	Year 1	Year 2	Year 3	Year 4	Year 5
ADA market share	0%	0%	0%	0%	0%
Patients receiving BSC	175	272	366	461	556
Total cost of patients receiving BSC	£113,843	£177,011	£237,801	£299,398	£361,797

The incremental budget impact of the introduction of ADA is presented in Table 23.

Table 23: Incremental budget impact of the introduction of ADA.

	Year 1	Year 2	Year 3	Year 4	Year 5
Total costs with introduction of ADA	£1,664,854	£2,526,969	£3,381,754	£4,249,624	£5,128,794
Total costs without introduction of ADA	£113,843	£177,011	£237,801	£299,398	£361,797
Incremental overall budget impact	£1,551,011	£2,349,958	£3,143,953	£3,950,226	£4,766,996

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OZURDEX® (dexamethasone intravitreal implant) for the treatment of posterior segment uveitis

NICE multiple technology appraisal submission by Allergan

Submitted on: 19 August 2016

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Executive Summary

Uveitis is a long-term inflammatory condition and is the fifth most common cause of vision loss in the developed world. It accounts for 10–15% of all cases of vision loss and up to one-fifth of cases of legal blindness. This appraisal focuses on non-infectious posterior segment uveitis, which refers to uveitis that affect areas of the eye posterior to the lens; the term therefore includes intermediate and posterior uveitis and panuveitis. Posterior segment uveitis accounts for about a quarter of all cases of uveitis. It is less common than anterior uveitis, but, as acknowledged in the scope, it is more severe and is more likely to cause vision loss.

Posterior segment uveitis typically affects people of working age (20–60 years), with incidence peaking in the 40–45 age group but falling significantly after the age of 70 years. An estimated 1,500–5,000 people are diagnosed with non-infectious intermediate or posterior uveitis in England each year (an estimate for the incidence of panuveitis was not found).

About 40% of people with uveitis of any type have severe bilateral disease; however, estimates vary and are complicated by the development of bilateral disease over time.

Patients with posterior segment uveitis face significant loss of vision and have a diminished health-related quality of life (HRQL) compared with the general population, particularly in aspects of mental health. Uveitis also compromises work productivity, contributing to the overall economic burden, which also includes increased direct healthcare costs.

The burden of uveitis is substantial in itself and is exacerbated by the fact that older, but still commonly used, treatments (high-dose systemic corticosteroids and immunosuppressants) have questionable effectiveness, are poorly tolerated, and are associated with side effects. Furthermore, the need for frequent administration and intensive management of side effects imposes a considerable burden on the patient as well as cost to the National Health Service (NHS). Access to newer treatments, including Ozurdex®, has been hampered by funding restrictions, which vary by geography. There is considerable evidence of "postcode prescribing", and patients in a number of areas are left without access to treatment options if systemic corticosteroid therapy fails. The difficulties in accessing funding for Ozurdex® for posterior segment uveitis provides the rationale for its inclusion in the scope of this current NICE appraisal.

Ozurdex® (hereafter referred to as DEX 700) is a dexamethasone intravitreal implant. It was the first pharmacological therapy licensed for the local treatment of non-infectious posterior segment uveitis in adults. Dexamethasone is released slowly, providing a total dose of approximately 700 µg. DEX 700 is licensed by the European Medicines Agency (EMA) for the treatment of adult patients with:

- visual impairment due to diabetic macular oedema (DMO) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy
- macular oedema following either branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)
- inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

DEX 700 was launched in the UK in August 2010 for the treatment of adult patients with macular oedema following BRVO or CRVO. The licence was extended in June 2011 to include the treatment of adult patients with non-infectious uveitis affecting the posterior segment of the eye, and in August 2014 for the treatment of DMO in August 2014. NICE has recommended DEX 700 for the treatment

of retinal vein occlusion (RVO; July 2011) and DMO (July 2015). The current submission provides information pertinent only to the posterior segment uveitis indication.

There is a high unmet need for treatments for posterior segment uveitis that are effective in reducing inflammation but without the significant side effects associated with long-term use of high-dose systemic corticosteroids and immunosuppressants. DEX 700 provides sustained and localised release of dexamethasone into the eye, avoiding the need for systemic therapy or frequent injections.

The clinical value of DEX 700 in posterior segment uveitis has been demonstrated in the pivotal HURON study, a 26 week randomised controlled phase III trial; patients received either DEX 700 or a sham treatment involving a needleless applicator. The trial demonstrated the following benefits of DEX 700.

- DEX 700 had a beneficial impact on vision gain: a significantly greater proportion of patients treated with DEX 700 achieved an improvement in best corrected visual acuity (BCVA) of ≥ 15 letters compared with sham from baseline to week 8 ($P < 0.001$). This improvement was maintained for the duration of the trial.
- DEX 700 was also superior to sham in terms of vitreous haze: vitreous haze score 0 at week 8 (the primary endpoint) was achieved in 47% of eyes treated with DEX 700, compared with 12% in the sham group ($P < 0.001$).
- The superior efficacy of DEX 700 was evident as early as week 3 and continued throughout the 26-week study over a broad range of efficacy endpoints.
- DEX 700 provided a significantly greater reduction in mean central retinal thickness than sham at week 8 ($P \leq 0.004$).
- The HURON study also demonstrated that DEX 700 is well tolerated: there were no significant difference in the overall adverse event rates between DEX 700 and sham.

The efficacy of DEX 700 was supported by statistically significant and clinically meaningful improvements in vision-related HRQL, demonstrated by improvements in several subscales of the National Eye Institute (NEI) Visual Function Questionnaire-25 (VFQ-25) and the composite score: the mean improvement in the overall composite score at week 8 was 11.62 with DEX 700, compared with 3.42 with sham ($P < 0.001$). Furthermore, 60.9% of patients treated with DEX 700 had ≥ 5 point improvement in the overall composite score, compared with 29.0% with sham ($P < 0.001$), and 50.7% achieved ≥ 10-point improvement with DEX 700, compared with 15.9% with sham ($P < 0.001$).

DEX 700 has been extensively studied in long term non-randomised retrospective studies in clinical practice, involving 14–84 eyes, conducted across a wide range of geographical locations. These studies have consistently reported rapid and sustained effectiveness of DEX 700 in the treatment of non-infectious posterior segment uveitis across a range of measures, including improvements in BCVA, central retinal thickness, and vitreous haze score.

DEX 700 is effective with repeated implantation, with a median duration of effect of approximately 6 months, for bilateral implantation, in patients who have previously received systemic therapies, and in those with pars plana vitrectomy (PPV). DEX 700 also allowed systemic therapies to be discontinued, or the dose reduced, in a large proportion of patients (44–78%) in real-world clinical practice. Real-world studies have demonstrated the efficacy of DEX 700 in a broader patient population than that included in HURON. Differences in the magnitude of clinical response between real-world studies and HURON reflect differences in inclusion criteria; however, DEX 700 has

consistently shown significant clinical benefit in patients with posterior segment uveitis, in both trials and real-world clinical settings.

Although use of DEX 700 is known to increase intraocular pressure (IOP), this was a transient and manageable effect in HURON. In the HURON study, the proportion of patients in the DEX 700 group with IOP values ≥ 25 mmHg was low throughout the study, peaking at week 3 (7.1% [5 patients]), before falling to 4.1% (3 patients) at week 8, and 0% at week 26. The proportion of patients with IOP ≥ 35 mmHg was even lower, with a maximum of 4.1% (3 patients) at week 12 and 0% at week 26.

The proportion of patients with an increase in IOP ≥ 10 mmHg was significantly greater with DEX 700 than sham only at week 8. Such increases either did not require treatment or were managed with topical IOP-lowering medications. No patients in the HURON trial required incisional surgery for glaucoma.

Cataract was reported as an adverse event in 9 of 62 phakic eyes (15%) in the DEX 700 group and 4 of 55 phakic eyes (7%) in the sham group (P = 0.769) in the HURON trial. Three patients had a surgical procedure for cataract in the study eye (one eye in the DEX 700 group and two in the sham group).

Real-world studies have reported a low incidence of adverse events following treatment with DEX 700. Small increases in IOP have been reported in patients receiving DEX 700, although the mean IOP usually remained within normal limits. IOP ≥ 25 mmHg was more common in baseline steroid responders and in eyes without prior PPV. The proportion of patients with increased IOP is typically higher in real-world studies, reflecting the inclusion of patients with prior need for IOP-lowering medications, who were excluded from HURON. Incidence of cataracts following treatment with DEX 700 was low in all identified real-world studies. Implant migration to the anterior chamber has been reported in very few patients and occurred in aphakic or pseudophakic eyes. Very few cases of endophthalmitis or retinal detachment were reported after administration of DEX 700.

The UK list price for DEX 700 is £870 for the implant and applicator (excluding valued added tax). It is assumed that the intravitreal implant is administered in the outpatient setting, at a cost of £109 per implant procedure. The mean number of implants per eye has been estimated at 1.64 over 12 months in real-world clinical practice. The mean annual drug cost for DEX 700 is calculated to be £1,427 for unilateral treatment and £2,854 for bilateral treatment, £95 for systemic prednisolone (10 mg daily), £272 for mycophenolate mofetil (2 g daily), and £1,626 for systemic tacrolimus (4 mg daily). Monitoring costs are higher with the systemic therapies, which partially offset the higher drug and administration costs of DEX 700. Costs associated with adverse events with systemic therapy – which for systemic corticosteroids include the development of diabetes and osteoporosis and for systemic immunosuppressant include excess cancer cases – are difficult to estimate but are likely to be high.

An estimated 589 patients with posterior segment uveitis that has not responded systemic corticosteroids would be eligible for treatment with DEX 700 in England and Wales. The net budget impact of using DEX 700 rather than systemic corticosteroids or immunosuppressants for these patients depends on which treatments are displaced. If it assumed that all eligible patients are treated with DEX 700 rather than prednisolone, the cumulative net budget impact would be £5.5 million over 5 years, based on 30% of patients requiring bilateral treatment. Replacing mycophenolate mofetil with DEX 700 would have a cumulative net budget impact of £4.6 million, and replacing tacrolimus with DEX 700 would have a cumulative net budget impact of £0.6 million.

These estimates do not include the costs of treating adverse events associated with the long-term use of any of these treatments, however; inclusion of these costs, which are difficult to quantify from the available evidence base, are likely to favour DEX 700, given the high frequency of adverse events with systemic treatments, and their potentially chronic and serious nature, and the low incidence of IOP or cataract seen for DEX 700 in HURON and real-world studies.

This submission does not include a cost–utility model for DEX 700 in the treatment of posterior segment uveitis. A favourable cost–utility profile was shown for DEX 700 in the treatment of RVO, supporting a recommendation by NICE in that indication. The cost per patient associated with DEX 700 treatment is comparable for the two conditions, while the absolute and incremental gains in visual acuity – which in turn are closely correlated with vision-related HRQL – are greater in patients with posterior segment uveitis than in those with RVO. On this basis, it is reasonable to assume that DEX 700 would represent a cost-effective use of NHS resources in the treatment of posterior segment uveitis, according to NICE's usual criteria.

In conclusion, DEX 700 is an effective and well-tolerated option for the treatment of posterior segment uveitis. Its use is already established in the NHS – to the extent permitted by current funding restrictions. DEX 700 provides an attractive option for patients in whom systemic corticosteroids have failed or where the alternative is increasingly high doses, which in turn raises the risk of more serious side effects. The net budget impact compared with such therapy is modest and is likely to be over-estimated, given the difficulty of accurately capturing the costs of managing the costs associated with systemic corticosteroid treatment.

1 Background and context

1.1 Background to posterior segment uveitis

Uveitis can be either infectious or non-infectious and is also classified according to the location of inflammation.

- Anterior uveitis is inflammation of the iris; this is the most common type of uveitis, accounting for three-quarters of all cases.
- Posterior segment uveitis – the focus of this multiple technology appraisal (MTA) – refers to uveitis that affect areas of the eye posterior to the lens; it includes intermediate uveitis, posterior uveitis and panuveitis. Intermediate uveitis affects the middle of the eye, including the vitreous (vitritis) and peripheral retina; posterior uveitis primarily affects the retina or choroid and may be secondarily associated with vitritis; panuveitis affects all areas of the uveal tract.

Non-infectious uveitis may be due to an underlying inflammatory condition, an autoimmune disorder or trauma to the eye.

1.2 Epidemiology

Population-based epidemiology studies for uveitis are sparse but are important because reports from referral centres may not provide an accurate depiction of the overall spectrum of the severity of uveitis because only patients with disease are referred to specialist clinics (1).

According to data relating to onset of symptoms in 3000 patients from a tertiary referral centre in Manchester, uveitis usually affects people aged 20–60 years (2). The incidence of uveitis increases with age, peaking in the 40–45 year age group and declining significantly after 70 years of age.

An estimated 1,500–5,000 people are diagnosed with non-infectious posterior segment uveitis in England each year (3) – calculated from estimates available in 2010 which gave a prevalence of 3–10 cases of posterior segment uveitis per 100,000 population. However, no estimates for the incidence of panuveitis are available, according to the NICE draft scope (4).

Only one UK-based study was identified that provides estimates for the prevalence of uveitis, based on the number of people receiving systemic immunosuppression (corticosteroids or immunosuppressants) for uveitis based on prescription data from health boards (5). The study identified 363 patients in Scotland who received systemic therapy for uveitis in 2005. The mean age of the patient population was 46.4 years. NHS Grampian health board recorded a prevalence of 25 per 100,000, which was considered to be the most robust estimate because it included all uveitis cases being followed up at a specialist inflammatory eye clinic in this health board region. It is difficult to compare estimates from this study with other population-based studies because the Scottish study assessed only systemically treated uveitis. A study of Kaiser Permanente plan members in Northern California, USA, estimated an overall prevalence of 115.3 per 100,000; this is considered the most appropriate source of prevalence estimates for this appraisal as it is based on a large population-based sample (6). However, this study includes people with uveitis affecting any area of the eye.

In terms of anatomical location, uveitis affected the posterior segment of the eye in 14% of patients in the epidemiology study in Northern California (6). This estimate was calculated by including intermediate, posterior and diffuse uveitis but excluded anterior uveitis and uveitis of indeterminate location. Applying this estimate of 14% to the overall prevalence of uveitis in this study gives an estimated prevalence for posterior segment uveitis of 16 per 100,000 in the Californian study. By contrast, the Manchester study found that 54% of patients had intermediate or posterior uveitis or panuveitis (2), which is likely to reflect the greater severity of posterior segment uveitis compared with anterior uveitis, which is more likely to be managed in other settings, rather than being referred to this tertiary clinic. It is therefore estimated that the prevalence of posterior segment uveitis in England would be 16 per 100,000 of the adult population, based on the estimated prevalence in the Northern California study.

Bodaghi 2005 estimated that 41.3% of cases of severe uveitis are bilateral; however, we did not find estimates for the proportion of cases of non-infectious posterior uveitis that are bilateral and whether this proportion changes with increased severity.

The Manchester study assessed the prevalence of comorbid systemic signs and symptoms upon presentation at the clinic: 67.4% of patients had no systemic signs or symptoms (2). Among those with systemic signs or symptoms, arthropathy was the most common (13.6%) (Table 1).

Table 1 Comorbid systemic signs and symptoms in patients presenting at the Manchester uveitis clinic (2)

System	Proportion with comorbid symptom or sign n=3000
No symptoms/signs	67.4
Arthropathy	13.6
Skin lesions	9.1
Chest	6.4
Neurological	5.1
Bowel disorder	3.0

Given that there are few epidemiology studies of uveitis in the UK, these are likely to be the best estimates of the proportion of patients who are affected by systemic comorbidities. The authors of the study noted that this was the largest single-centre survey on uveitis worldwide. However, caution should be exercised in terms of the applicability of all aspects of this evidence base to DEX 700, since the Manchester study included patients with a broad range of uveitis subtypes who would be outside the indication for DEX 700 (i.e., patients with anterior uveitis or uveitis of infectious origin, and juvenile patients).

1.3 Disease burden

The burden of uveitis is substantial: it is the fifth most common cause of vision loss in the developed world, accounting for 10–15% of all cases of vision loss and up to 20% of cases of visual blindness (7). Suttorp-Schulten and Rothova (1996) assessed the causes and frequency of blindness in patients with uveitis in a study of 582 patients in the Netherlands (8). Patients were followed up for a mean of 4.3 years. The data presented in Table 2 indicate that visual impairment and blindness are significant risks for patients with uveitis, particularly for those with the intermediate or posterior

form: 28% of patients with intermediate uveitis developed either visual impairment or legal blindness in one or both eyes, rising to 46% for those with posterior uveitis.

Table 2 Visual outcomes in patients with uveitis (8)

	Visual impairment		Legal blindness	
	Unilateral	**Bilateral**	**Unilateral**	**Bilateral**
Anterior uveitis (n = 246)	13 (5)	7 (3)	22 (9)	4 (2)
Intermediate uveitis (n = 78)	10 (13)	4 (5)	8 (10)	0 (0)
Posterior uveitis (n = 129)	20 (16)	3 (2)	28 (22)	8 (6)
Panuveitis (n = 107)	19 (12)	20 (19)	21 (19)	10 (9)
Total (n = 582)	64 (11)	35 (6)	82 (14)	22 (4)

Legal blindness is defined as < 0.1 best corrected visual acuity (BCVA) for the better eye; visual impairment is defined as ≤ 0.3 BCVA for the eye with better vision; 26 patients with legal blindness in one eye and visual impairment in the other eye were categorised as having bilateral visual impairment.
Values are n (%).

1.3.1 Economic and societal burden

Uveitis can impose a significant economic and societal burden through direct healthcare costs and impact on work productivity (increased absenteeism, reduced productivity while at work, and early retirement due to ill health). Given the age profile of patients with uveitis affecting the posterior segment of the eye, Thorne and colleagues (2016) have hypothesised that the work productivity burden would be greater than in patients with blindness or vision impairment due to age-related ocular diseases (9). Thorne and colleagues determined the direct and indirect costs associated with uveitis in a retrospective claims database analysis of privately insured people in the US. Healthcare utilisation and costs were analysed in a prevalent sample of patients with non-infectious posterior segment uveitis, and work productivity was analysed in a longitudinal sample of incident cases. In the prevalent sample, a subgroup of patients requiring persistent uveitis therapy was defined based on use of corticosteroids, non-biologic immunosuppressants or biologic therapy for ≥ 90 days. Cases were matched 1:1 with controls who did not have uveitis, matched for sex, age, region and index date. Cases and controls were required to have data for 6 months prior to and 12 months after the index date. The index date was randomly selected as a point during the baseline or follow-up period, allowing assessment of patients at a variety of points in the disease course. Patient records were considered during the period 1998–2012.

These data indicate that uveitis was associated with consistently higher resource use compared with matched controls across all resource utilisation categories (Table 3). Furthermore, resource utilisation was higher in patients with persistent uveitis than in matched controls and compared with the “all uveitis” patient population (statistical difference not reported).

Table 3 Annual healthcare resource utilisation in patients with uveitis in a retrospective study (9)

Annual mean visits/ number of drugs used	All uveitis		Persistent uveitis	
	Cases (n=705)	Controls (n=705)	Cases (n=112)	Controls (n=112)
Inpatient stays	0.2[a]	0.1	0.3[b]	0.1
Emergency department visit	0.4[a]	0.2	0.6[b]	0.1
Outpatient/ other visit	16.5[a]	7.6	26.3[a]	9.4
Ophthalmologist/ optometrist visit	3.6[a]	0.3	6.6[a]	0.5
Any prescription drugs	7.8[a]	4.1	13.3[a]	4.5

Persistent uveitis was defined based on use of corticosteroids, non-biologic immunosuppressants or biologic therapy for ≥ 90 days.
[a] $P < 0.0001$. [b] $P < 0.05$.

Resource use was also converted into 2012 US$ costs (Table 4). Annual mean direct healthcare costs were 5.1 times higher for the persistent uveitis group than for controls. Prescription drug costs were 6.9 times higher, and non-drug medical costs were 4.3 times higher ($P < 0.05$ for all comparisons with matched controls).

Table 4 Annual mean direct health care costs associated with uveitis in a retrospective study (9)

	All uveitis		Persistent uveitis	
	Cases	Controls	Cases	Controls
Non-drug medical costs	7,790	2,645	15,933	3,682
Prescription drug costs	5,151	1,085	10,345	1,499
Total direct costs	12,940	3,730	26,279	5,181

Costs are in 2012 USD.

Thorne and colleagues also considered the impact of uveitis on work productivity (9). One full day of work loss was assumed for each hospitalisation and emergency department visit, and 0.5 day for each outpatient visit, taking into account travel and waiting time. A mean of 18.7 work days were lost in the uveitis group, compared with 8.4 work days in matched controls ($P < 0.0001$). Work productivity loss was higher in the persistent uveitis subgroup than in matched controls (35.5 vs 11.5 mean days lost; $P < 0.0001$).

The availability of salary data in this US database allowed an accurate estimate of the cost of these work productivity losses. In the “all uveitis” group, total indirect costs were 2.3 times higher than for matched controls ($3,144 vs $1,378; $P < 0.0001$). When the analysis was restricted to the persistent uveitis subgroup, the total indirect costs were 3.6 times higher in the cases compared with the controls ($6,624 vs $1,816; $P < 0.0001$) (9).

Kaplan–Meier analyses without adjustment for demographics and clinical characteristics showed that incident uveitis cases were at significantly increased risk of leaving the workforce for any reason during follow-up compared with matched controls ($P = 0.007$, log-rank test). The 10 year probability

of leaving the workforce was 44% for uveitis cases, compared with 33% for matched controls. Cox regression models, controlling for patient demographics and clinical characteristics, showed that uveitis cases were significantly more likely than controls to leave the workforce for any reason during follow-up (hazard ratio [HR] 1.27; P = 0.04).

The impact of uveitis on retirement is important, given the mean age of 44.7 years for the incident patient cohort. However, Thorne and colleagues did not have data for the incident cohort of patients with persistent uveitis so it is not known whether persistent uveitis increases the risk of early retirement. The extent to which systemic comorbidities account for the higher direct and indirect costs in uveitis patients in this study compared with matched controls is not clear.

1.3.2 Impact on HRQL

In terms of the humanistic burden of uveitis, vision loss has been reported to have a substantial effect on health-related qualify of life (HRQL). Naik and colleagues (2013) considered the impact of uveitis on vision-related functioning and HRQL using baseline HRQL data from the HURON trial of DEX 700 (10). (Full details of this trial are presented in Section 2.4.) The baseline trial data allow consideration of the impact of uveitis on a range of HRQL domains that are affected by vision loss. The uveitis population had clinically significant impairments in vision-specific functioning compared with a normal-vision US population assessed during development of the National Eye Institute (NEI) Visual Function Questionnaire-25 (VFQ-25) (11). Differences > 10 points were seen between the HURON uveitis population and the normal-vision population across all 11 VFQ-25 domains and the composite scores (all P < 0.001). The authors reported that results were similar for intermediate and posterior uveitis classifications.

HRQL baseline scores from HURON have also been compared with US general population scores obtained from the National Health Measurement Survey (NHMS). Mean scores of the HURON uveitis population on the short-form health survey (SF-36, SF-6D), and EuroQol five-dimension (EQ-5D) questionnaires were compared with age-, sex-, and race-matched subjects from the NHMS US general population dataset. The HURON uveitis population had lower mean scores on a number of subscales of the SF-36: role-emotional, mental health, role-physical, vitality, general health, and mental component summary ($p<0.05$). Scores for the physical component summary, physical functioning, bodily pain, and social functioning were similar in the two populations, however, suggesting that uveitis caused a greater impairment of mental than physical components (Table 5).

The HURON uveitis population also had a statistically significantly worse SF-6D mean score than the NHMS US general population, but similar mean EQ-5D index scores, indicating that the SF-6D may be more sensitive to differences in vision-related HRQL impairments due to uveitis than the EQ-5D index score valued using the US tariff.

Table 5 Baseline SF-36, SF-6D, and EQ-5D scores from the HURON trial compared with US general population (10)

SF-36 item/ SF-6D/ EQ-5D	HURON trial	US general population	P value[a]
Physical component summary	47.7 (12.2)	48.9 (10.4)	0.27
Mental component summary	47.6 (12.7)	53.3 (9.6)	<0.001
Physical functioning	79.7 (23.8)	83.6 (25.5)	0.10
Role-physical	65.5 (40.7)	81.4 (25.0)	<0.001
Bodily pain	71.3 (23.3)	71.3 (24.5)	0.99
General health	64.7 (21.5)	70.1 (22.6)	0.01
Vitality	57.8 (22.5)	65.0 (20.8)	<0.001
Social functioning	82.3 (25.3)	86.4 (22.6)	0.06
Role-emotional	74.7 (39.5)	89.8 (19.8)	<0.001
Mental health	72.3 (19.0)	81.3 (17.2)	<0.001
SF-6D	0.67 (0.11)	0.78 (0.14)	<0.001
EQ-5D index (US tariff)	0.84 (0.13)	0.85 (0.17)	0.56

Values are mean (SD) scores.
[a] Two-sided t-test for independent groups.

Naik et al (2013) were also able to assess the impact of uveitis on HRQL compared with other eye conditions. VFQ-25 subscale scores were lower in patients with intermediate and posterior uveitis than in patients with diabetic retinopathy, age-related macular degeneration, glaucoma, cataract or cytomegalovirus retinitis.

These data highlight the impact of uveitis on HRQL. It is reasonable to hypothesise that the impact of vision loss on HRQL is likely to be a consistent regardless of the underlying disease cause, and that the greater impact on HRQL reported for intermediate and posterior uveitis may be associated with systemic treatment and its side effects. Further research would be useful to test this hypothesis. The data nevertheless indicate that, whether related directly to uveitis or to the medications used to treat it, uveitis impairs mental health and wellbeing compared with the general population.

1.4 Ozurdex®

Ozurdex® (DEX 700) is an intravitreal implant containing 700 µg of dexamethasone (12). DEX 700 is indicated by the European Medicines Agency (EMA) for the treatment of adult patients with:

- visual impairment due to diabetic macular oedema (DMO) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy
- macular oedema following either branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)
- inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

DEX 700 is the first pharmacological therapy licensed for the local treatment of adults with non-infectious posterior segment uveitis. It was launched in the UK in August 2010 for the treatment of adult patients with macular oedema following either BRVO or CRVO. The licence was extended in June 2010 to include the treatment of adult patients with non-infectious uveitis affecting the posterior segment of the eye, and in August 2014 for the treatment of DMO. NICE recommended

DEX 700 for the treatment of RVO and DMO in guidance issued in July 2011 and July 2015, respectively.

This submission covers only the indication of non-infectious uveitis affecting the posterior segment of the eye, as detailed in the scope for this MTA. DEX 700 originally received an orphan designation from the EMA for the treatment of non-infectious uveitis affecting the posterior segment of the eye but the application for orphan designation was later withdrawn because DEX 700 is marketed for non-orphan indications that affect larger patient populations, as outlined above.

The recommended dose is one implant, administered intravitreally to the affected eye. Administration to both eyes concurrently is not recommended according to the Summary of Product Characteristics (SPC). Repeat doses should be considered if a patient experiences a response to treatment followed by a loss in visual acuity (VA), and if, in the physician's opinion, the patient may benefit. Patients who experience and retain improved vision should not be re-treated. Patients who experience deterioration in vision that is not slowed by DEX 700 should also not be re-treated.

1.5 Innovation

DEX 700 is delivered via a posterior segment drug delivery system that releases dexamethasone slowly over time, providing a total dose of approximately 700 µg. The implant is injected into the eye via the pars plana, using a specially designed applicator. The implant is composed of an inactive biodegradable polymer matrix of poly [lactic-glycolic] acid containing micronised dexamethasone (60/40 drug/polymer ratio) which is slowly released from the polymer.

The pharmacokinetic benefits of the delivery system are described in a review by Whitcup and Robinson (2015) (13). Briefly, after intravitreal injection, dexamethasone is cleared rapidly from the eye, with an estimated half-life of 5.5 hours in human eyes. By contrast, pharmacokinetic studies performed in the eyes of male monkeys have demonstrated that, after a single DEX 700 administration, the concentrations of dexamethasone in the retina and vitreous peak within 1–2 months and remain detectable for 6 months after treatment. The mean concentration of dexamethasone in the retina and vitreous at day 60, was 1110 ng/g and 213 ng/mL, respectively. Mean plasma concentrations were low through to day 60 (1.1 ng/mL), after which they were below the limit of quantitation. The gradual degradation of the polymer over time negates the need to remove the implant.

Other routes of administration require much higher daily doses of dexamethasone to achieve therapeutic levels of the drug in the posterior segment of the eye while exposing non-target areas of the body to corticosteroids. These pharmacokinetic results demonstrate the sustained and localised presence of dexamethasone in the eye after treatment with DEX 700. This allows localised treatment of the eye without the need for regular injections required for the administration of a dexamethasone solution, the therapeutic effects of which would be expected to last no longer than a few days. Although the pharmacokinetics of DEX 700 has not been studied in human eyes, the results from monkeys are consistent with the clinical effects in human eyes with uveitis (described in Section 2).

It can therefore be seen that DEX 700 provides a novel method for delivering the drug to the target area over a sustained period. The benefits of this innovation are less frequent injections into the eye and a reduction in systemic exposure to corticosteroids. The costs avoided by avoidance of the side effects of high-dose systemic corticosteroids, such as osteoporotic fractures, can, in theory, be

calculated but may not be included in modelled cost estimates for systemic corticosteroid use. In addition, the HRQL benefits of less frequent injections and avoidance of the side effects associated with high-dose systemic corticosteroids can, in theory, also be calculated for inclusion in estimates of quality-adjusted life-years. However, estimates of their impact on utility are not available. Based on this, it is unlikely that the innovative benefits of DEX 700 would be fully captured in the modelling of costs and benefits.

1.6 Treatment positioning

The treatment of posterior segment uveitis is defined by the Department of Health a specialised service. The service has been commissioned by NHS England because:

- the number of individuals requiring the service is small
- the cost of providing the service is high because of the specialist interventions involved
- the number of doctors and other expert staff trained to deliver the service is small
- the cost of treating some patients is high, placing a potential financial risk on individual clinical commissioning groups (CCGs).

NHS England has not developed an overall national commissioning policy in this area. In practice, commissioning and funding policies relating to the use of DEX 700 for posterior segment uveitis have been developed in some areas but not others. This has resulted in considerable variation in access to DEX 700 in different parts of the NHS ("postcode prescribing").

1.6.1 Local treatment guidelines

Local treatment guidelines are available for the North East of England (14). These guidelines recommend that DEX 700 should be administered every 6 months. If bilateral treatment is required, each eye should be treated in separate treatment episodes, in order to minimise the consequences of procedural complications. Where inflammation is asymmetric, the ophthalmologist should consider treating only the more severely affected eye. These guidelines indicate that DEX 700 should be reserved for sight-threatening or sight-losing intermediate or posterior uveitis.

The guidelines note that clinicians should consider whether a patient should receive a systemic treatment for uveitis, for example those with severe bilateral uveitis and those with very active associated systemic disease. If the patient's uveitis remains uncontrolled despite an adequate trial of systemic therapies and periocular corticosteroid injections, DEX 700 is recommended as follows:

- Where systemic treatment has been tried but the patient is intolerant following an adequate trial at typical treatment doses, clinicians should consider whether treatment intolerance(s) can be managed without necessitating discontinuation.
- Where systemic treatments are contraindicated, clinicians should consider whether an alternative systemic treatment could be used before commencing treatment with DEX 700.
- DEX 700 is recommended for:
    - patients with no underlying associated systemic inflammatory disease and those whose associated underlying systemic inflammatory disease is of limited activity and does not require systemic treatment
    - patients with severe unilateral uveitis.

The guidelines also recommend that treatment is discontinued in the following circumstances:

- if there is any loss of VA from baseline values
- if there is little or no effect on inflammatory symptoms and signs
- when a systemic treatment is commenced that is likely to have a beneficial effect on the uveitis; DEX 700 should only be recommenced after it has been ascertained that no beneficial effect from the systemic treatment has occurred
- if intraocular pressure (IOP) in the treated eye is severely raised, or if moderately raised IOP in the treated eye is considered to be related to DEX 700.

In addition, in the presence of limited anti-inflammatory effect, clinicians should consider whether continuation with DEX 700 is appropriate if the maximal gain in VA is < 5 letters on a standard sight chart, as this indicates only a limited benefit of treatment.

In Allergan's view, these guidelines represent an overall balanced view of the advantages and disadvantages of DEX 700. However, the recommended frequency of DEX 700 to be given every six months per eye should not be viewed as a strict requirement to wait for at least six months before re-treatment. Zarranz-Ventura et al. indicates that for patients requiring a second implant in the same eye the mean time to re-treatment is 6.6 months (median 6 months) among patients with 12-month follow up, but there is variation in the time to re-treatment among patients (SD 1.9 months) (15).

Recommendations for use of DEX 700 should recognise that individual patients may require flexibility in the re-treatment dosing interval and some patients would be under-treated if the requirement was to wait for a minimum of 6 months, even if this would be clinically appropriate for a majority. The requirement for a trial of periocular corticosteroid injections as an earlier line of therapy before DEX 700 is not considered appropriate, given that there are no licensed periocular injection therapies and Kenalog® (triamcinolone) is contraindicated for this use. Furthermore, Allergan considers that it may also be overly restrictive to allow use of DEX 700 only after failure of systemic immunosuppressant therapy. It would be appropriate for DEX 700 to be considered as a second-line alternative to systemic immunosuppressant therapy, particularly given the risks associated with long-term use of systemic immunosuppressant therapies.

Finally, Allergan considers that where patients experience moderately elevated IOP that is considered to be treatment-related, it would be more appropriate to consider treatment with IOP-lowering medication before any decision is made to discontinue DEX 700 therapy. It should be borne in mind that posterior segment uveitis is more threatening to an individual's sight than elevated IOP.

The North East Retinal Group guidelines appear to be the basis for guidelines used by the NHS Southern Derbyshire CCG, as the wording of the recommendations is similar except for the following points relating to treatment continuation criteria (16). The Southern Derbyshire CCG guidelines indicate that funding for DEX 700 will only be maintained for ongoing treatment where it can be demonstrated that:

- there is a ≥ 15 letter (0.3 logMAR) improvement in best corrected visual acuity (BCVA) 12 weeks after the first administration, or the patient achieves driving VA (20/40 on the Snellen scale; 0.3 logMAR)
- VA is maintained at ≥ 50% of the best recorded following diagnosis of uveitis.

Allergan considers these treatment continuation criteria to be overly restrictive. The requirement to achieve a 15-letter improvement in BCVA may not be possible in patients with a pre-existing cataract or central macular oedema although these patients would still benefit from DEX 700 therapy. Similarly, patients may be given DEX 700 because systemic corticosteroid or immunosuppressant therapy has to be stopped because of intolerance. In this group of patients, the disease may be reasonably controlled at the time of the first DEX 700 implant, so a large gain in BCVA would not be expected. Therefore, there may be a range of clinical circumstances in which a patient would achieve a substantial benefit from DEX 700 therapy but without achieving a 15-letter improvement in BCVA.

It should be noted that the treatment guidelines described above position DEX 700 as a therapeutic option for patients in whom systemic steroids have failed or in whom increased doses to control relapse are not appropriate. Allergan believes that DEX 700 can be positioned as an option for patients with acute inflammation, since this would limit systemic steroid exposure and the associated severe side effects. Furthermore, patients with diabetes or mental health disorders may not be considered for short-term high-dose steroid use; DEX 700 may offer a therapeutic option for acute posterior segment uveitis in these patients.

1.7 Comparators

Topical corticosteroids can be effective treatments for anterior uveitis but have poor bioavailability in the areas of the eye affected by posterior segment uveitis, which limits their use for this indication. Therefore, topical corticosteroids are not an appropriate comparator for the dexamethasone implant for patients with confirmed posterior segment uveitis, as detailed in the final scope for this appraisal. The roles of the various comparators listed in the final appraisal scope are outlined in the following section.

1.7.1 Periocular or intravitreal corticosteroid injections

Periocular and intravitreal corticosteroid injections have been used to deliver a greater concentration of corticosteroids to the posterior segment of the eye than is feasible with systemic corticosteroids. Triamcinolone acetonide is one of the most commonly used formulations for periocular or intravitreal injection. However, all commercially available formulations of triamcinolone acetate in the UK are contraindicated for intraocular use. According to the SPC for triamcinolone acetonide intra-articular/intramuscular injection (Kenalog) “Adequate studies to demonstrate the safety of Kenalog use by intra-turbinal, subconjunctival, sub-tenons, retrobulbar and intraocular (intravitreal) injections have not been performed. Endophthalmitis, eye inflammation, increased IOP, and visual disturbances including vision loss have been reported with intravitreal administration” (17).

Allergan therefore does not consider triamcinolone periocular and intravitreal injections to be an appropriate comparator for this appraisal. A search of the clinicaltrials.gov website did not identify any completed randomised controlled trials (RCTs) of periocular or intravitreal corticosteroid injections for uveitis. The only identified ongoing trial of periocular or intravitreal corticosteroids was for triamcinolone. Details of this trial are outlined in Section 2.7 but it is not due to complete until 2018.

Kenalog (triamcinolone acetonide) is specifically contraindicated for ocular use, and Allergan considers that it is not possible to characterise appropriately the comparative safety and efficacy of any periocular or intravitreal corticosteroid injection, given the lack of published safety and efficacy RCT data. Furthermore, the chronic nature of uveitis means that numerous repeat injections may be required. Depending on the frequency of injections, this may represent a time, travel and inconvenience burden to patients and family members, and potentially increases the risk of injection complications. Furthermore, the cost to the NHS would not be negligible once administration costs are taken into account, even though the drug cost may be small. The North East Treatment Advisory Group report in 2012 estimated an annual cost of £2,500 per eye to inject triamcinolone, based on an assumption of four injections per year (18).

1.7.2 Intravitreal corticosteroid implants

DEX 700 is the only intravitreal corticosteroid implant that is both licensed and available in the UK for the treatment of posterior segment uveitis. An implant containing 190 µg fluocinolone acetonide is licensed for the treatment of chronic DMO (Iluvien®) (19). However, this implant is not licensed for the treatment of uveitis. A 590 µg fluocinolone acetonide implant (Retisert®) for non-infectious uveitis was under consideration by the EMA but was withdrawn in 2007 (20). According to the EMA "based on the review of the data, at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that RETISERT could not have been approved for the treatment of chronic non-infectious uveitis" (21). The EMA also noted "that a benefit of Retisert had not been demonstrated based on the two-year results presented in the application, since the patients receiving Retisert in the main study did not have a longer time until their disease came back than those taking standard care. In addition, the Committee did not consider the main measure of effectiveness to be appropriate for this type of study. The use of Retisert was also linked to side effects, including eye pain, increased pressure within the eyeball and cataracts, which led to vision problems in some patients. There were also concerns over the quality of the medicine. Therefore, at the time of the withdrawal, the CHMP's view was that a benefit of Retisert had not been sufficiently demonstrated and any benefits did not outweigh the identified risks" (21).

Licensed or commercially available intravitreal implants containing triamcinolone acetonide are not available in the UK. Allergan considers that the lack of licensed corticosteroid intravitreal implants means that none of these therapies should be considered as an appropriate comparator for DEX 700.

1.7.3 Systemic corticosteroids

Oral prednisolone is the most commonly used systemic corticosteroid and, because of its efficacy and cost, it is likely to constitute first-line therapy for the majority of patients with non-infectious uveitis. However, patients requiring long-term treatment with systemic corticosteroids are at risk of significant side effects, as outlined in Section 4. Therefore, patients should not be maintained on high-dose corticosteroid therapy for the treatment of posterior segment uveitis over the long term. Guidelines developed by the Scottish Uveitis National Managed Clinical Network state that all patients who require long-term steroids > 7.5 mg per day should be considered for immunosuppressive therapy to allow reduction in the steroid therapy (22).

In view of this, it may be considered that systemic corticosteroids are not a comparator to DEX 700 in terms of the decision problem, because either systemic corticosteroid therapy will have failed before trying DEX 700, or systemic corticosteroid therapy will be considered inappropriate. Therefore, if low-dose systemic corticosteroid maintenance therapy fails, best supportive care will be considered. This means that long-term high-dose systemic corticosteroid therapy is not a relevant comparator, because high-dose systemic corticosteroid would only be used in the short term as first-line therapy; if a dose > 7.5 mg prednisolone per day is required, alternative steroid-sparing therapies would be used (22).

1.7.4 Systemic immunosuppressant therapies including azathioprine, methotrexate, cyclophosphamide, ciclosporin, chlorambucil, tacrolimus, mycophenolate mofetil and TNF-alpha inhibitors

Data are not available for the proportions of patients who receive systemic immunosuppressive therapy options for the treatment of posterior segment uveitis in the UK. However, clinical expert opinion (personal communication) indicates that mycophenolate mofetil and tacrolimus are the most commonly used systemic immunosuppressants in UK centres. It should also be noted that adalimumab is the only licensed biologic immunosuppressant for the treatment of non-infectious uveitis. Methotrexate, cyclophosphamide, ciclosporin, and chlorambucil are not commonly used given the availability of alternatives that are considered to have a better risk–benefit profile, principally mycophenolate mofetil and tacrolimus. Mycophenolate mofetil and tacrolimus are used as second-line treatment options after failure of systemic corticosteroids (including for patients who require high doses that cannot be maintained safely in the long term).

Given the lower drug acquisition costs for mycophenolate mofetil and tacrolimus, the use of DEX 700 has been reserved in local UK treatment guidelines for after failure of a systemic immunosuppressant. However, due to the risk of side effects with long-term immunosuppressant therapy it may be considered that treatment with DEX 700 should be the preferred second line therapy option for patients failing first line systemic corticosteroids.

It is challenging to compare the efficacy of DEX 700 and mycophenolate mofetil or tacrolimus because of the absence of safety and efficacy RCT data for these immunosuppressants in the treatment of posterior segment uveitis. A search of the clinical trials.gov website identified only two RCTs of systemic immunosuppressants. The Multicentre Uveitis Steroid Treatment (MUST) trial randomised patients to either systemic immunosuppressant therapy or fluocinolone intravitreal surgical implant (23). A range of immunosuppressant therapies were permitted, so the results are not specific to any particular drug. The trial found that mean VA improved in both arms. At 24 months, 21% vs 13% of eyes with posterior segment uveitis assigned to implant or systemic therapy, respectively, had gained ≥ 15 letters (3 lines, 0.3 logMAR) of VA (P = 0.065). In terms of AEs, over 24 months, eyes treated with an implant had a higher risk of cataract surgery (80% vs 31% among those at risk; HR 3.3, P < 0.0001), treatment for elevated IOP (61% vs 20%; HR 4.2, P < 0.0001) and glaucoma (17% vs 4%; HR 4.2, P = 0.0008). Patients who received systematic treatment had more prescription-requiring infections (0.60 vs 0.36 per person-year, P = 0.034) but there was no significant difference in the rate of hospitalisation.

The second trial identified was a small trial conducted in India which randomised patients with intermediate, posterior, or panuveitis requiring corticosteroid-sparing therapy to either mycophenolate mofetil or methotrexate (24). Among the 80 patients randomised in the trial, 67 (35

methotrexate and 32 mycophenolate mofetil) completed the study or were classified as treatment failures prior to the 6 month visit. The study authors note that due to low power a larger multinational study with similar design is being conducted and is due for completion in 2018 (NCT01829295). Overall, given the paucity of RCT data it is difficult to assess the comparative safety and efficacy of systemic immunosuppressant therapies vs DEX 700 for the treatment of posterior segment uveitis.

Adalimumab is the only TNF inhibitor licensed for the treatment of uveitis. However, the licence specifies its use after failure of corticosteroids, and the need for annual assessment of its risk–benefit profile for ongoing treatment. It is therefore anticipated that, as an intravitreal corticosteroid option, DEX 700 would be used before adalimumab is considered. Adalimumab would be considered for patients with significant systemic involvement. Therefore, adalimumab is more likely to be used as a second-line option for patients requiring treatment for systemic involvement or as a third-line option after failure of systemic and intravitreal corticosteroids in patients without systemic involvement.

1.7.5 Intravitreal methotrexate

Intravitreal methotrexate is not licensed for the treatment of uveitis. A search of the clinicaltrials.gov website identified only one trial of interest in uveitis (NCT02623426), an ongoing trial comparing intravitreal methotrexate versus DEX 700 versus intravitreal ranibizumab for uveitic macular oedema. Only small retrospective studies of intravitreal methotrexate use are available (25); given the paucity of RCT data and the absence of a licence, it is therefore difficult to compare the efficacy and safety of intravitreal methotrexate and DEX 700.

1.7.6 Best supportive care (when all other treatment options have been tried)

Best supportive care is specified in the NICE scope at the end of the treatment pathway, when all other treatment options have been tried; it is therefore unlikely to be a comparator for DEX 700. However, best supportive care may be the appropriate comparator for second-line treatment following failure of systemic corticosteroids in a subgroup of patients in whom systemic non-biologic or biologic immunosuppressants are inappropriate or contraindicated because of the risk of systemic side effects.

1.8 Unmet need

As noted in Section 1.3, uveitis is associated with a substantial burden, accounting for 10–15% of cases of vision loss in the Western world. Patient numbers are small but those with posterior segment uveitis face a significant risk of either partial or complete vision loss, with all the associated costs and impact on HRQL.

A number of therapies are used in the NHS for the treatment of posterior segment uveitis, including DEX 700. Each option has significant limitations, however, resulting in unmet need. Systemic corticosteroid or immunosuppressant treatments tend to be prioritised both in available NHS guidelines and in practice, and do not generally face access barriers because of drug acquisition cost. Both of these categories of treatment, however, are compromised by their AE profile and alternative treatment options are needed for patients whose uveitis does not respond adequately to these treatments. There is therefore a need for treatments that are effective in reducing inflammation without significant side effects associated with long-term high dose use of systemic corticosteroids and systemic immunosuppressant therapies. This level of unmet need was recognised by the

granting of orphan designation for DEX 700 by the EMA in 2010 (26) (although this designation was subsequently withdrawn because DEX 700 was already marketed for other indications with a broader population).

As detailed in Sections 2 and 3 of this submission, DEX 700 has been shown to be effective in the treatment of posterior segment uveitis and has an acceptable and manageable side-effect profile. It is used in NHS practice and is recommended as a second- or third-line treatment in the few published regional/local NHS guidelines. Nevertheless, access remains restricted and variable because of funding restrictions, giving rise to an unacceptable "postcode lottery". Patients living in areas where access to DEX 700 is not funded or commissioned, and who would otherwise be appropriate for treatment, face a significant clinical need which, for financial reasons, the NHS does not currently meet. It is in this context that this NICE appraisal is taking place.

2 Clinical effectiveness

2.1 Overview of the dexamethasone implant clinical development programme

DEX 700 was first licensed by the EMA on 27 July 2010, for the treatment of adults with macular oedema following BRVO or CRVO, as part of the centralised procedure. Two phase III studies were conducted for these indications (206207-008 and 206207-009) (27, 28). A phase II dose-ranging study using 350 and 700 µg tableted DEX was conducted in patients with persistent macular oedema associated with diabetic retinopathy, uveitis, RVO, or Irvine–Gass syndrome (DC103-06) (29, 30). The study included a subgroup of 14 patients with uveitis. The results from this study led to doses of 350 µg and 700 µg being taken forward into phase III development for posterior segment uveitis. The licence extension for the treatment of adult patients with non-infectious posterior segment uveitis was supported by one pivotal phase III study (206207-014; HURON). The EMA did not consider DC103-06 further when assessing the efficacy of DEX 700, however, because of the small number of patients. A phase III study for the treatment of anterior uveitis was also planned but was terminated after only five patients had been enrolled, and is not discussed further. The EMA provided scientific advice before commencement of the pivotal HURON trial: "the sample size and 6-month study duration were considered to be sufficient for safety purposes since longer term safety information will be provided from the completed RVO studies and the ongoing masked repeat-dose studies in diabetic macular oedema (DMO)" (26).

2.2 Identification of clinical evidence

The PubMed database (Medline) was searched for studies reporting clinical efficacy and safety outcomes in patients treated with DEX 700, using the following search terms: ((("dexamethasone"[MeSH Terms] OR "dexamethasone"[All Fields]) AND intravitreal[All Fields] AND implant[All Fields]) OR ozurdex[All Fields]) AND ("uveitis"[MeSH Terms] OR "uveitis"[All Fields]).

The search yielded 92 results. Additional searches were conducted of clinical trial registries in Europe (EudraCT) and the US (clinicaltrials.gov):

- EudraCT was searched for the terms “uveitis AND dexamethasone”, identifying six studies
- clinicaltrials.gov was searched using the terms “uveitis” AND “dexamethasone”, identifying 22 trials.

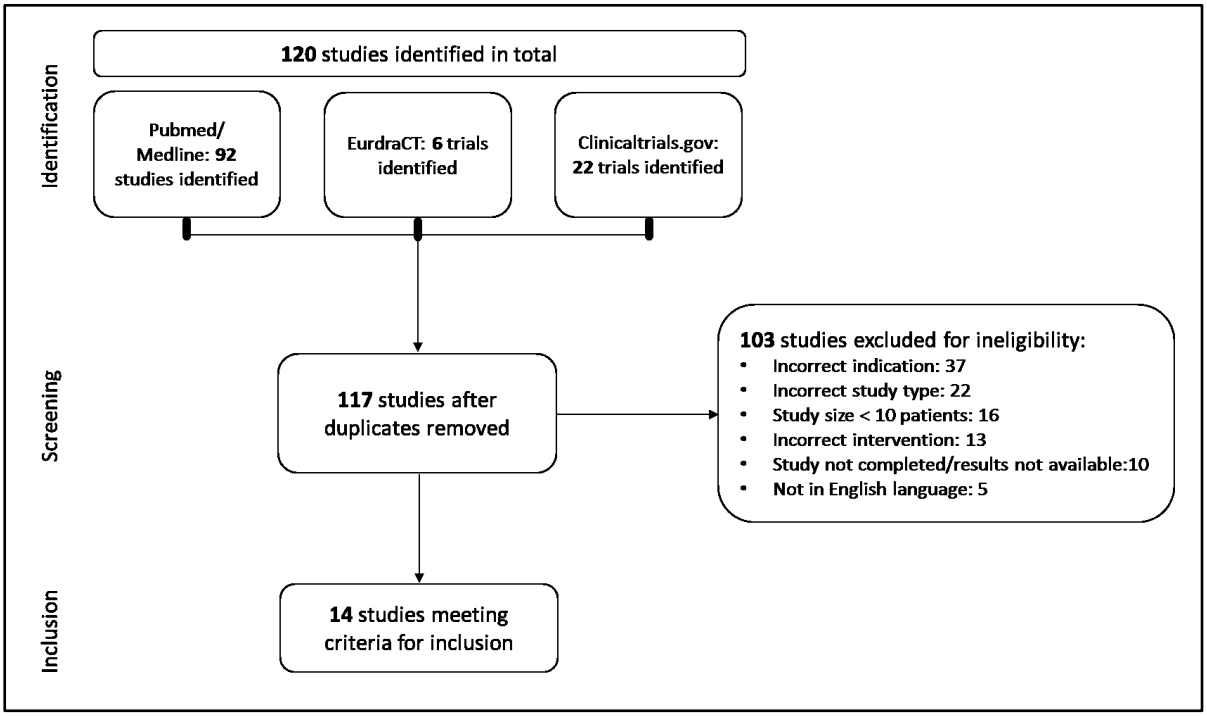
A total of 120 studies were identified from the three searches. Two of the results were found to be same trial (clinicaltrials.gov identifier NCT00333814; EudraCT identifier: 2006-000736-26) which were both the Allergan-sponsored HURON trial (sponsor ID: 206207-14). This study is also the subject of two publications identified in the PubMed review. Furthermore, NCT01870440/NCRVA-2013-Ozurdex-16.2 was listed on clinicaltrials.gov as providing results presented in one of these publications. These three results from clinical trials database searches were therefore excluded as duplicates.

After exclusion of duplicates, the abstracts and titles, or trial database summaries, of the remaining 117 studies were reviewed to exclude studies that did not meet the following criteria:

- Indication: non-infectious uveitis affecting the posterior segment of the eye
- intervention: DEX 700 (Ozurdex)
- study size: at least 10 patients
- study type: reporting clinical efficacy and/or safety outcomes in humans
- study completed and results available
- language: English.

After screening abstracts and titles, 103 studies were considered ineligible and were excluded; 14 studies were selected for full text review and inclusion. The selection of studies for review is presented in Figure 1.

Figure 1 PRISMA diagram showing selection of studies for review of the clinical efficacy and safety of DEX 700



One of the studies excluded during screening (incorrect study type) was a Cochrane systematic review by Brady et al (31). The search outputs from this systematic review were screened but no further studies were identified for inclusion. However, it should be noted that Brady and colleagues limited their searches to studies comparing outcomes with current standard of care treatments, with a minimum follow-up of 6 months.

A long-term safety study examining the use of DEX 700 in real-world clinical practice was identified in the search of clinicaltrials.gov (NCT01539577; sponsor ID: 206207-025). The primary completion date was March 2016 but this study is included in the list of ongoing studies since results are not yet available.

The pivotal phase III HURON RCT (NCT00333814; EudraCT 2006-000736-26; Allergan-sponsored ID: 206207-14) has been used as the primary source of efficacy and safety data. Data have been taken from the clinical study report (32) and three trial publications which were identified in the PubMed search (10, 33, 34). This trial compared outcomes in eyes treated with 700 µg or 350 µg dexamethasone intravitreal implants (DEX 700 and DEX 350, respectively) with eyes that underwent a sham procedure. Marketing authorisation is for DEX 700; the data for this dose therefore form the basis of this submission, in line with the protocol outlined by the NICE assessment group for this appraisal. However, data for both doses are presented for the primary efficacy outcome (proportion of patients with vitreous haze score 0) and for the overview of AEs in the HURON trial. These data demonstrate that DEX 700 provides additional efficacy compared with DEX 350 with a similar safety profile. All other efficacy and safety data presented from the HURON trial show a comparison of DEX 700 with the sham control. All non-randomised studies reported relate to the commercially available DEX 700.

Further searches of Allergan internal databases did not identify any other manufacturer-sponsored clinical trials for inclusion.

2.3 Overview of clinical effectiveness

- The HURON trial was the pivotal phase III RCT that provided the data to support regulatory approval of DEX 700 for the treatment of non-infectious posterior segment uveitis.
- The HURON trial demonstrated a consistent, rapid, and sustained clinical benefit with DEX 700 compared with sham treatment.
    - DEX 700 demonstrated superior efficacy to sham as early as week 3, which continued throughout the 26 week study over a broad range of efficacy variables. A significantly higher proportion of patients who received DEX 700 achieved a ≥ 15 letter improvement in BCVA and mean improvement from baseline BCVA at all study visits, from week 3 to 26.
    - DEX 700 was superior to sham at the week 8 primary time point in the proportion of patients with vitreous haze score 0 (the primary endpoint).
    - DEX 700 was numerically superior to DEX 350 for almost all efficacy variables and time points.
    - The efficacy of DEX 700 was supported by statistically significant and clinically meaningful improvements of 5–10 points from baseline in several VFQ-25 subscales and the composite score. A dose–response trend was seen in most domains, with greater improvements in the DEX 700 group.

    - Rescue medications were required by 1.3% of patients in the DEX 700 group at 3 weeks post-implantation, increasing to 22.1% at 26 weeks, compared with 14.5% at 3 weeks and 38.3% at 26 weeks in the sham group.
- Non-randomised retrospective studies of 14–84 eyes, conducted across a wide range of geographical locations, have consistently reported the rapid and sustained clinical effectiveness of DEX 700 in the treatment of non-infectious posterior segment uveitis, based on a range of measures, including improvements in BCVA, central retinal thickness (CRT), and vitreous haze score.
    - Tomkins-Netzer and colleagues (2014) (35) reported that repeat implantation in the same eye, and bilateral implantation, was as effective as first implantation in a cohort of patients from UK clinical practice.
    - Zarranz-Ventura and colleagues (2014) (15) reported results, including patients from UK clinical practice, demonstrating that DEX 700 is effective in the treatment of cystoid macular oedema resulting from anterior or posterior segment uveitis. Furthermore, DEX 700 treatment allowed reduction of systemic corticosteroid or immunosuppressive therapy over time in some patients.
    - Adan and colleagues (2013) (36) reported that DEX 700 provided clinical benefit in patients who had undergone prior PPV, whereas Pelegrin and colleagues (2015) (37) reported that outcomes were better in eyes that had not undergone PPV.
    - Khurana and Porco (2015) (38) reported that eyes without an epiretinal membrane at baseline benefited from treatment with DEX 700.
    - Across multiple studies, the time to treatment failure or relapse of macular oedema was approximately 6 months, and the median time to repeat implantation of DEX 700 ranged from 4.7 to 10 months. Outcomes and duration of response were similar after repeat implantations.
    - Pleyer and colleagues (2014) reported that a reduction in the dose of systemic corticosteroids – or discontinuation – was possible within a 24 week follow-up in 44% of patients who received a single DEX 700 implant in German clinical practice (39). Pelegrin et al (2015) demonstrated a reduction in the dose of systemic therapies in 100% of patients at 1 month post-implantation, which was maintained in 78% of patients at 12 months post-implantation; discontinuation of prednisone was possible in 32% of patients (37).
    - Clinical outcomes were similar in eyes with posterior or intermediate uveitis (39).

2.4 Efficacy results from the HURON study

All details of the HURON trial are taken from the clinical study report (32) unless otherwise specified. Additional sources include three trial publications (10, 33, 34).

2.4.1 HURON study: methods

2.4.1.1 Study objectives

The objective of the HURON study was to evaluate the safety and efficacy of the 700 µg and 350 µg DEX PS DDS Applicator Systems (referred to as DEX 700 and DEX 350) compared with a sham DEX PS DDS Applicator System (needleless applicator) in the treatment of non-infectious ocular inflammation of the posterior segment in patients with intermediate or posterior uveitis.

2.4.1.2 Study design (HURON)

HURON was an 8 week multicentre, masked, randomised, sham-controlled, parallel-group, safety and efficacy study with an 18 week masked extension. Patients were randomised in a 1:1:1 ratio to receive DEX 700, DEX 350, or a sham application. Approximately 231 patients were to be randomised in order to have 219 patients complete the study at week 8, based on an anticipated dropout rate of 5%. Patients were stratified into two strata at randomisation according to their baseline scores for vitreous haze: +1.5 or +2, and +3 or +4.

The baseline visit occurred within 4–14 days after the screening visit. Patients underwent the treatment procedure at the treatment visit (day 0), which was on the same day as the baseline visit or up to 4 days later. The study coordinator or treating investigator contacted the patient on day 1 for a post-procedure telephone follow-up, which was followed by a post-procedure safety visit on day 7. Masked outcome assessment visits occurred at weeks 3, 6, 8, 12, 16, 20, and 26. Note that some patients may have had additional visits at day 1 and weeks 2, 4, and 5. A patient was considered to have exited from the study upon completion of week 26 or early study discontinuation.

The treating investigator performed the implant placement and other treatment procedures and was responsible for the overall safety of study participants, but kept all study medication information confidential and did not collect efficacy information. Patients were masked with regard to study treatment, and the key efficacy variables were recorded and evaluated by follow-up investigators who were also masked with regard to study treatment.

Efficacy variables included vitreous haze score, BCVA, CRT (measured by optical coherence tomography [OCT] at selected sites only), and use of rescue medications. Safety variables were AEs, BCVA, IOP, biomicroscopy, and ophthalmoscopy.

The null hypothesis for the primary efficacy analysis was that there was no difference between DEX 700 and sham in the proportion of patients whose vitreous haze score decreased to 0 in the study eye at week 8. The alternative hypothesis was that there existed a difference between the two treatment groups. Similar hypotheses applied to the comparison of DEX 350 versus sham.

2.4.1.3 Selection of patient population

Patients with a diagnosis of non-infectious intermediate or posterior uveitis in at least one eye were enrolled into this study. Only one eye (identified as the study eye) was treated during the study. The study eye was identified at screening, confirmed at baseline, and remained the same throughout the study. If both eyes were eligible for the study, the right eye was designated as the study eye.

For enrolment into the study, patients had to meet all the inclusion criteria and none of the exclusion criteria detailed in Table 6.

Table 6 Inclusion and exclusion criteria for the HURON study

Inclusion criteria
• Male or female, at least 18 years of age. • Diagnosis of intermediate or posterior uveitis in at least one eye based on the standardisation of uveitis nomenclature for reporting clinical data workshop (SUN Working Group 2005). For diagnosis of intermediate uveitis (e.g. pars planitis, posterior cyclitis, hyalitis), the vitreous must have been the primary site of inflammation. The presence of peripheral vascular sheathing and macular oedema was acceptable as long as the vitreous remained the main site of inflammation. For diagnosis of posterior

uveitis, the retina or choroid must have been the primary site of inflammation. Suspected masquerade syndromes should have been ruled out by the investigator prior to patient entry into the study.

- Vitreous haze of at least +1.5 at both the screening and baseline visits in the study eye.
- Best corrected ETDRS VA core of 10–75 letters inclusive (Snellen equivalent approximately 20/640–20/32) at screening and baseline visits in the study eye.
- Media clarity other than vitreous haze, pupillary dilation, and patient cooperation sufficient for adequate visualization in the study eye.
- Allowable treatments at screening, baseline, and treatment (day 0) visits:
  - Topical corticosteroids and non-steroidal anti-inflammatory drugs (e.g., ketorolac, diclofenac) if doses were stable for at least 2 weeks prior to screening and were to remain stable through treatment (day 0).
  - Systemic immunosuppression (e.g., ciclosporin, methotrexate) if doses were stable for at least 3 months prior to screening and were to remain stable through treatment (day 0).
  - Systemic corticosteroids if doses were ≤ 20 mg/day oral prednisone (or equivalent), were stable for at least 1 month prior to screening, and were to remain stable through treatment (day 0).
  - Topical cycloplegia (e.g., homatropine, atropine) at the investigator's discretion.
- Female patients of childbearing potential must have had a negative urine pregnancy test at the treatment visit.

General exclusion criteria

- Female patients who were pregnant, nursing or planning a pregnancy, or who were of childbearing potential and not using a reliable means of contraception.
- Uncontrolled systemic disease or known HIV infection.
- Participation in an investigational trial within 30 days of study entry.
- Use of warfarin/heparin/enoxaparin or similar anticoagulant agent ≤ 2 weeks prior to the treatment (day 0) visit.
- Known allergy or sensitivity to the study medication(s), any component of the delivery vehicle, any corticosteroids or any diagnostic agents used during the study (e.g., fluorescein, dilation drops).
- Anticipated need to initiate or change doses of current systemic immunosuppression or systemic corticosteroids during the first 8 weeks of the study.
- Any condition (including inability to read VA charts or language barrier) that precluded the patient's ability to comply with study requirements, including completion of the study.
- Patient had a condition or was in a situation that, in the investigator's opinion, may have put the patient at significant risk, may have confounded the study results, or may have interfered significantly with the patient's participation in the study.

Ocular exclusion criteria

- Previous enrolment in a DEX PS DDS clinical trial.
- IOP > 21 mmHg at screening or baseline.
- History of clinically significant IOP elevation in response to corticosteroid treatment in either eye (defined as an increase > 10 mmHg and an absolute IOP ≥ 25 mmHg without the use of antiglaucoma medications) unless there was a functioning trabeculectomy or seton (with IOP < 18 mmHg at screening and baseline) and there was no significant visual field loss in the investigator's opinion.
- History, diagnosis or clinical findings of ocular hypertension or glaucoma (e.g., elevated IOP, optic nerve head change consistent with glaucoma, glaucomatous visual field loss) in the study eye unless there was a functioning trabeculectomy or seton (with IOP < 18 mmHg at screening and baseline) and there was no significant visual field loss in the investigator's opinion. Patients with a history of episodic increases in IOP due to inflammation and not due to corticosteroids may have been eligible if they met all other IOP and glaucoma medication exclusions.
- Use of antiglaucoma medications in the study eye within 4 weeks prior to the screening visit or any use between screening and treatment visits.
- History of central serous chorioretinopathy in either eye.
- Any active ocular infection (i.e., bacterial, viral, parasitic or fungal) in either eye at screening, baseline or treatment visits.
- Presence of active or inactive toxoplasmosis in either eye.
- Contraindication to pupil dilation in either eye.

- Any other ocular disease (e.g., choroidal neovascularisation, media opacity) in the study eye that could have interfered with the diagnosis or assessment of disease progression.
- Periocular corticosteroid injections to the study eye ≤ 8 weeks prior to the treatment visit.
- History of any intravitreal drug injection to the study eye ≤ 26 weeks prior to the treatment visit.
- History of any intravitreal corticosteroid injection to the study eye unless all the following criteria were met:
  - the only corticosteroid injected intravitreally was triamcinolone acetonide
  - the most recent dose was > 26 weeks prior to the treatment visit
  - all doses were ≤ 4 mg.
- Any previous use of Retisert (fluocinolone acetonide intravitreal implant) in the study eye.
- Intraocular surgery, including cataract surgery and/or laser of any type, in the study eye ≤ 90 days prior to the treatment.
- Aphakia or anterior chamber intraocular lens in the study eye (posterior chamber intraocular lens was acceptable).
- History of pars plana vitrectomy in the study eye.
- History of herpetic infection in the study eye or adnexa.
- Presence of visible scleral thinning or ectasia in the study eye at screening, baseline or treatment visits.
- Best corrected ETDRS VA score < 34 letters (approximately 20/200 on the Snellen scale) in the non-study eye using the ETDRS method at the screening or baseline visit.
- Uveitis expected to be unresponsive to corticosteroids or uveitis unresponsive to prior corticosteroids.
- Hypotony (IOP < 5 mmHg or clinical signs such as choroidals, choroidal, or corneal folds) or prephthisis (e.g., scleral thickening on ultrasonography, decreasing globe size).

2.4.1.4 Treatments

Only one eye was treated with study drug. Patients received DEX 700, DEX 350 or sham on the randomisation day 0 visit. The study treatment procedure was performed by the treating investigator in a surgical suite or office setting, using a standard sterile technique. A combination of topical and subconjunctival anaesthesia was used. Patients randomised to active treatment had the study drug placed into the vitreous through the pars plana using the DEX PS DDS Applicator System. Patients randomised to sham treatment had the needleless applicator pressed against the conjunctiva. Patients were also given peri-operative anti-infective treatment.

2.4.1.5 Rescue medications

Immediate intervention by the investigator was allowed for patients whose intraocular inflammation worsened after the study treatment procedure. These patients could receive other therapy to control their uveitis, at the investigator's discretion, and were followed up to the end of the study at 26 weeks. Rescue medications were defined as intravitreal/periocular injections of corticosteroids in the study eye or systemic medications (e.g. oral or intravenous) taken for uveitis or ocular inflammation which were newly started or increased in dose from treatment day 0.

2.4.1.6 Primary efficacy measurements

The primary efficacy variable was the vitreous haze score. The ophthalmologist graded the vitreous haze by viewing the optic disc and posterior retina using an indirect ophthalmoscope set to large beam and mid-power illumination with a 20-diopter lens. Low ambient lighting and the same indirect ophthalmoscope were used whenever possible. The view was compared against a published photographic standardised scale (Nussenblatt et al, 1985), which was modified to include a +1.5 grade. Vitreous haze was graded as follows:

0	No inflammation
+0.5	Trace inflammation (slight blurring of the optic disc margins and/or loss of the nerve fibre layer reflex)
+1	Mild blurring of retinal vessels and optic nerve
+1.5	Optic nerve head and posterior retina view obscuration > +1, but < +2
+2	Moderate blurring of optic nerve head
+3	Marked blurring of optic nerve head
+4	Optic nerve head not visible

2.4.1.7 Secondary efficacy measurements

2.4.1.7.1 BCVA

BCVA was measured using the Age Related Eye Disease Study Research Group (AREDS) modification of the Early Treatment Diabetic Retinopathy Study Group (ETDRS) method (AREDS report no. 8, 2001). Lighthouse or precision distance VA charts mounted on a retro-illuminated box providing standardised illumination were used. Refraction was used for determination of BCVA and was performed using a standard technique. Different charts were used for refraction and BCVA measurement of each eye. VA testing was performed at 4 metres, and at 1 metre for patients with sufficiently reduced vision.

BCVA was measured following manifest refraction except on days 1 and 7. On those days, VA evaluations may have been performed using the refraction obtained at the screening or baseline visit. The VA evaluations performed on days 1 and 7 were considered to be safety rather than efficacy measures; all other VA evaluations were considered to be both safety and efficacy measures.

2.4.1.7.2 Optical coherence tomography

OCT is a non-invasive laser-based diagnostic system that provides high-resolution images of the retina and retinal thickness. OCT was performed on the study eye only, at selected sites and using specified Allergan-approved equipment. At least six radial scans through the macula, each approximately 6 mm in length, were taken. Given that the vitreous opacity could have degraded the retinal image, the adequacy of the image was evaluated based on the signal strength and/or the investigator's clinical judgment.

2.4.1.8 Health related quality of life

Health related quality of life (HRQL) was assessed using the NEI VFQ-25, SF-36 (version 1), and the EQ-5D 3L; the SF-36 and EQ-5D were only administered at screening because they do not include vision-specific items.

The VFQ-25 is a shortened version of the 51-item NEI VFQ field test version. It consists of 25 vision-targeted questions that represent 11 vision-related quality of life subscales and one general health item. A coded value was applied to each item based on the original response, with a higher score representing better functionality.

The SF-36 is designed to represent eight important health concepts and a single question to assess patients' perceptions of their general health and wellbeing at present and compared with 1 year ago.

The EQ-5D consisted of a self-reported description of health status (EQ-5D self-classifier) and a visual analogue scale (VAS) thermometer for eliciting a self-rating of health status (EQ VAS).

The EQ-5D self-classifier captured a self-reported description of health problems on five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) using scores of 1 (none), 2 (some or moderate) and 3 (unable or extreme) for each. The EQ VAS has a range of 0–100, with 0 being the worst imaginable health state and 100 being the best imaginable health state.

2.4.1.9 Schedule of treatment visits and efficacy/HRQL assessments

The schedule of assessments for efficacy and HRQL measurements is shown in Table 7.

Table 7 Schedule of treatment visits and efficacy/HRQL assessments

	Screening*	Baseline*	Treatment*	Safety visit	Outcome assessment visits (weeks)						Final visit	
	Day −14 to −4	Day −4 to 0	Day 0	Day 7	3	6	8	12	16	20	26	Early exit
NEI VFQ-25	X						X		X		X	X
SF-36v1	X											
EQ-5D	X											
BCVA by ETDRS	X[a]	X[a]		X[b]	X	X	X[a]	X	X	X	X[a]	X[a]
Vitreous haze grading	FI[a]	FI[a]			FI	FI	FI[a]	FI	FI	FI	FI[a]	FI[a]
OCT (selected sites only)		X					X				X	X
Randomisation			X									
DEX PS DDS insertion/sham procedure			TI									
DEX PS DDS residual assessment											FI	FI

TI, Treating investigator; FI, Follow-up investigator (uveitis specialist); X, required assessment.

* Screening and baseline visits were 4–14 days apart; treatment visit may have occurred on the same day as the baseline visit or up to 4 days later.

[a] OU, oculus uterque (both eyes).

[b] BCVA performed using refraction obtained at screening or baseline visit.

2.4.1.10 Statistical and analytical plans

2.4.1.10.1 Analysis populations

There were three analysis populations: intent to treat (ITT), per protocol (PP), and safety.

- The ITT population included all randomised patients and was used for the efficacy analyses and summary of data other than safety variables.
- The PP population included all ITT patients who had no major protocol deviations and was also used for the efficacy analyses. The list of patients/visits to be excluded from the PP analysis was finalised prior to database lock.
- The safety population included all randomised and treated patients and was used in the analysis of all safety data.

In the ITT analyses, data were analysed according to the treatment patients were randomised to; for the PP and safety analyses, data were analysed according to the treatment patients actually received.

2.4.1.10.2 Primary efficacy analysis

The primary efficacy endpoint was the proportion of patients with vitreous haze score 0. Missing data at weeks 2 through 6, 8, 12, 16, 20 and 26 were imputed using the last observation (scheduled or unscheduled) carried forward (LOCF) method. All available data were used for imputation. For any patients who had received rescue medication, the vitreous haze score was set as missing at visits after the administration of rescue medication, and thus imputed by LOCF.

The primary efficacy analysis was performed using the ITT population based on scheduled visits, with week 8 being the primary time point. The primary analysis was performed using Pearson's chi-square test, and the primary comparisons of interest were DEX 700 versus sham and DEX 350 versus sham. A gate-keeping procedure was used to control the overall type I error rate at 5% for the two between-treatment comparisons (i.e., DEX 700 vs sham; DEX 350 vs sham). The comparison between DEX 700 and sham was performed first at the significance level of 0.05. If the comparison was statistically significant, the comparison between DEX 350 and sham was performed at the same significance level. If the comparison between DEX 700 and sham was not statistically significant, the DEX 350 and sham comparison was not considered statistically significant regardless of the P value.

In addition, two-sided 95% confidence intervals (CIs) were constructed for the between-group difference in the proportion of patients with vitreous haze score 0, using the normal approximation of binary variables. The treatment-by-investigator interaction was assessed using the Breslow–Day test at the significance level of 0.10. Any investigator with fewer than two patients enrolled in any treatment group was excluded from this analysis.

2.4.1.10.3 Secondary efficacy analyses

The two secondary efficacy analyses were performed using the ITT population. Efficacy measures after the administration of rescue medication were replaced by LOCF.

Time to vitreous haze score 0

Time to vitreous haze score 0 in the study eye was calculated from day 0 to the first occurrence of vitreous haze score 0 using the three scheduled visits at weeks 3, 6 and 8. For patients who did not achieve vitreous haze score 0 in the study eye at these visits, their time to vitreous haze score 0 was

censored at the last vitreous haze examination performed among these visits. Treatment group comparisons were analysed using the log-rank test.

In addition, the cumulative rates of achieving vitreous haze score 0 were calculated by the life-table method for weeks 3, 6, and 8. A two-sided Z-test and 95% CI were constructed to compare the cumulative rates at those scheduled visits, using the normal approximation. In the life-table analysis, the cumulative rates were calculated and displayed according to the intervals 0–3 weeks, 3–6 weeks and 6–8 weeks. Any scheduled visits occurring beyond day 70 (i.e., the upper limit of the week 8 visit window) were not included in the analysis.

Improvement in vitreous haze score ≥ 1 unit from baseline

Between-group differences were compared using a Pearson's chi-square test at the significance level of 0.05. Missing data were imputed using the LOCF (scheduled or unscheduled) method.

2.4.1.10.4 Other efficacy analyses

Unless otherwise stated, all other efficacy analyses were performed using the ITT population, based on the two-sided hypothesis test, with an unadjusted significance level of 0.05 and with missing data imputed using the LOCF (scheduled or unscheduled) method. Efficacy measures after rescue medication use were replaced by LOCF.

Mean vitreous haze score

Vitreous haze score for the study eye at each scheduled visit was analysed using a one-way analysis of variance (ANOVA) model, with fixed effect of treatment. Between-group comparisons were performed in a pairwise fashion using contrasts from the ANOVA model. A two-sided 95% CI was constructed for the between-group difference in mean vitreous haze scores for each of the three comparisons (i.e., DEX 700 vs sham; DEX 350 vs sham; DEX 700 vs DEX 350).

Change from baseline in vitreous haze score

Change from baseline in vitreous haze score for the study eye at each scheduled follow-up visit was analysed using the same methods as described for the mean vitreous haze score. In addition, within-group comparisons to baseline were performed using paired t-tests.

Responder analyses

Responder analyses were performed at each scheduled visit for the following endpoints:

- proportion of patients with ≥ 15 letter improvement in BCVA from baseline in the study eye
- proportion of patients with ≥ 10 letter improvement in BCVA from baseline in the study eye
- proportion of patients with ≥ 2 unit improvement in vitreous haze score from baseline in the study eye
- proportion of patients with ≥ 1 unit deterioration vitreous haze score from baseline in the study eye
- proportion of patients with at ≥ 2-unit deterioration from baseline vitreous haze score in the study eye.

In all responder analyses, pairwise between-group comparisons were performed using Pearson's chi-square or Fisher's exact test.

For BCVA, the VA score was set as the sum of 30 plus the number of letters read correctly, if the patient correctly read ≥ 20 letters at 4 metres. If the patient correctly read < 20 letters at 4 metres, VA was measured again at 1 metre. The VA score was set to the number of letters read correctly at

1 metre plus the number of letters read correctly at 4 metres. If VA was not measured at 1 metre in a patient who read < 20 letters correctly at 4 metres, the BCVA score was considered to be missing and was therefore imputed using LOCF.

Average retinal thickness

The average retinal thickness in 1.0 mm central macula of the study eye at baseline and the change from baseline in average retinal thickness at each scheduled follow-up visit were analysed using the same methods as for the mean vitreous haze score. Within-group comparisons versus baseline were performed using paired t-tests.

Summary of rescue medications

The proportion of patients who used rescue medication was summarised by visit. Pairwise between-group comparisons were performed using Pearson's chi-square or Fisher's exact test.

2.4.1.10.5 Subgroup analyses

The proportion of patients with vitreous haze score 0 in the study eye was analysed using the ITT population for the following subgroups: baseline vitreous haze score in the study eye (+1.5 and +2, +3 or +4), age (< 45, 45–65, > 65 years), sex (male, female), race (Caucasian and non-Caucasian), iris colour in the study eye (light [blue, green, hazel, other], dark [brown and black]), use of topical corticosteroids prior to day 0 (yes, no), use of systemic immunosuppressant and/or systemic corticosteroid medications prior to day 0 (yes, no); geographic region (North America, Brazil, Europe, Asia Pacific, Australia, Israel, India, South Africa), and investigator.

2.4.1.10.6 Analyses of health outcome questionnaires

VFQ-25

The summary score for each subscale was determined by taking the average across the multiple items within each corresponding subscale. The overall composite score was then calculated by averaging all 11 vision-targeted subscale scores, excluding the general health score. Items left blank were excluded from the calculation of average scores.

For VFQ-25 scores analysed as continuous variables, among- and between-group comparisons of raw scores and change from baseline values were performed using a one-way ANOVA model, with treatment as fixed effect. Responder analyses were conducted for each of the 11 subscales to assess the meaningfulness of change, using responder definitions of 5 point and 10 point improvements. The proportion of patients meeting the criterion for improvement in VFQ scores was compared between treatment groups using Pearson's chi-square test or Fisher's exact test.

SF-36

Each domain of the SF-36 generated a transformed score in the range 0–100 (0 being the worst score and 100 being the best). The eight SF-36 scales were standardised by means and standard deviations from the general US population and aggregated into two summary scores: the physical component summary and mental component summary. The transformed scores (0–100) for each of the eight domains and the two component summary scores were summarised descriptively. Among-group comparisons were performed using a one-way ANOVA model, with treatment as the fixed effect. Pairwise between-group comparisons were performed using a two-sample t-test if the among-group difference was statistically significant.

EQ-5D

For the EQ-5D self-classifier, the number and percent of patients in each response category was presented for each dimension. Among-group comparisons were performed using the Kruskal–Wallis test as ordered categorical results. Pairwise between-group comparisons were performed using the Wilcoxon rank-sum test if the among-group difference was statistically significant.

For EQ VAS data, descriptive statistics were presented and the among-group comparison was performed using a one-way ANOVA, with treatment as the fixed effect. Pairwise between-group comparisons were performed using the two-sample t-test if the among-group difference was statistically significant.

2.4.2 HURON study results

The primary endpoint of the HURON study for regulatory approval was the proportion of patients achieving vitreous haze score 0 at 8 weeks post-implantation. For consistency with the design of the trial, patient disposition, demographic and baseline characteristics, the primary efficacy outcome, and the rate of "any AE" are presented for all three study groups (DEX 700 vs DEX 350; DEX 700 vs sham; DEX 350 vs sham).

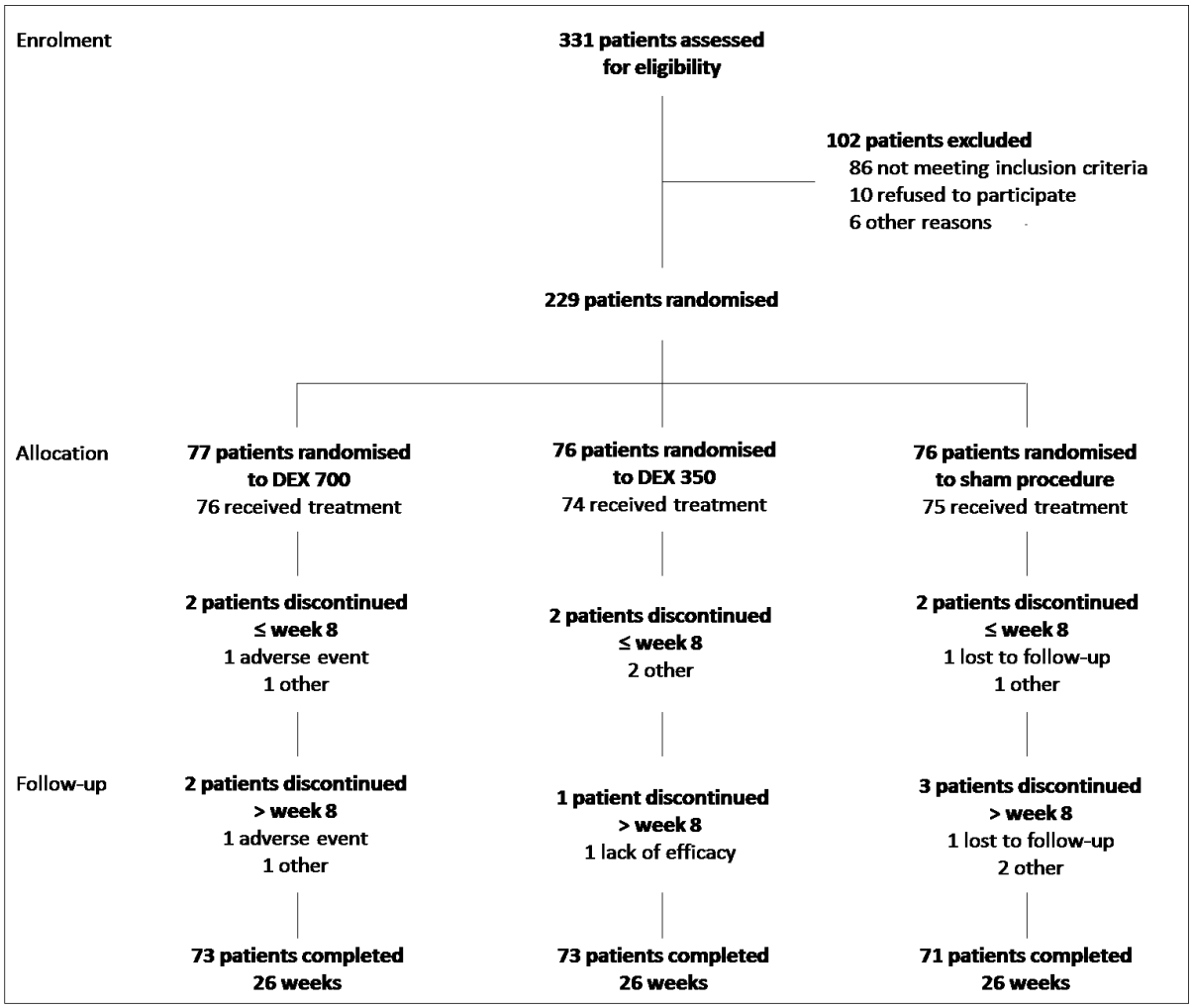
BCVA results are presented first as the most clinically relevant outcome of the HURON trial based on the appraisal scope. The BCVA results, along with the majority of other results presented in this submission, focus on the licensed dose of 700 μg (DEX 700).

2.4.2.1 Patient disposition

A total of 331 patients were screened, 102 of whom (30.8%) failed to meet the entry criteria: 21.1% because of inclusion criteria, 6.6% because of exclusion criteria, and 4.8% for other reasons.

A total of 229 patients from 46 study sites in 18 countries were randomised and enrolled in the study, as shown in Figure 2. Almost 95% of patients completed the 26 week study; the proportion of patients who completed the study was similar across the treatment groups.

Figure 2 Patient disposition in the HURON trial



2.4.2.2 Demographics and other baseline characteristics (HURON)

In the ITT population, the mean age was 44.8 years, 63.3% of patients were female, and 60.7% were Caucasian. The diagnosis was intermediate uveitis for 80.8% of patients and posterior uveitis for 19.2%. There were no statistically significant differences among the treatment groups in the demographic or baseline characteristics, as summarised in Table 8.

Table 8 Demographic and baseline characteristics in the HURON study (ITT population)

Characteristic	DEX 700 (n = 77)	DEX 350 (n = 76)	Sham (n = 76)	P value[a]
Age, years, mean (SD)	44 (14.8)	46 (13.6)	44 (15.0)	
Female	46 (59.7%)	48 (63.2%)	51 (67.1%)	
Race				
Caucasian	47 (61.0%)	46 (60.5%)	46 (60.5%)	0.997[b]
Black	8 (10.4%)	10 (13.2%)	9 (11.8%)	
Asian	18 (23.4%)	12 (15.8%)	15 (19.7%)	
Hispanic	2 (2.6%)	1 (1.3%)	2 (2.6%)	
Other	2 (2.6%)	7 (9.2%)	4 (5.3%)	
Iris colour				
Dark	33 (42.9%)	27 (35.5%)	32 (42.1%)	0.597
Light	44 (57.1%)	49 (64.5%)	44 (57.9%)	
Disease diagnosis				
Intermediate uveitis	63 (81.8%)	64 (84.2%)	58 (76.3%)	0.48
Posterior uveitis	14 (18.2%)	12 (15.8%)	18 (23.7%)	
Baseline visual acuity, letters, mean (SD)	58 (15.2)	57 (17.2)	63 (15.2)	0.071
Severity of vitreous haze at baseline				
Score of +1.5 or +2	65 (84%)	60 (79%)	66 (87%)	0.407
Score of +3 or +4	12 (16%)	16 (21%)	10 (13%)	
Baseline vitreous haze score, mean (SD)	2.06 (0.55)	2.12 (0.50)	2.01 (0.54)	0.427
Duration of uveitis, months, mean (SD)	50.5 (54.2)	43.9 (48.9)	61.2 (62.5)	0.154
Phakic lens at baseline	62 (81%)	51 (67%)	55 (72%)	0.194
Cataract in phakic eyes at baseline	20 (32%)	32 (63%)	27 (42%)	0.108
Patients taking systemic anti-inflammatory or immunosuppressant medication at baseline	20 (26%)	22 (29%)	18 (24%)	0.761

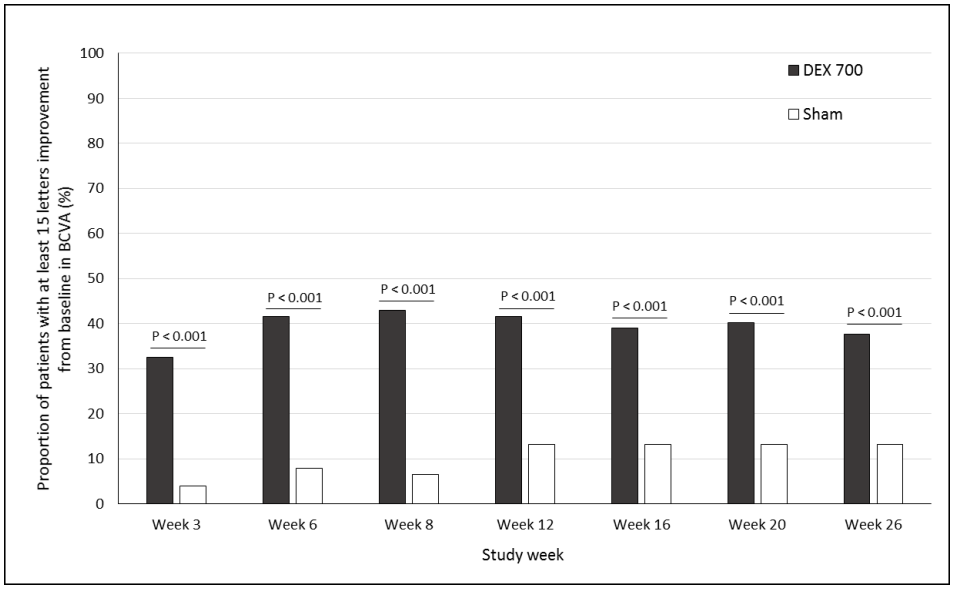
[a]P value based on one-way analysis of variance for continuous variables, and Pearson's chi-square or Fisher's exact test for categorical variables.
[b]Comparison of Caucasian vs non-Caucasian.

2.4.2.3 BCVA

2.4.2.3.1 Improvement of ≥ 15 letters from baseline

DEX 700 delivered a significant improvement in VA compared with sham as early as 3 weeks, and the improvement was maintained throughout the trial. At each visit, the proportion of patients with ≥ 15 letters (equivalent to 0.3 logMAR) improvement in BCVA from baseline was significantly higher with DEX 700 than with sham (P < 0.001). The proportion of patients demonstrating an improvement of ≥ 15 letters from baseline BCVA was more than twice to more than eight times higher with DEX 700 than with sham (Figure 3). The proportion of patients who achieved ≥ 15 letters improvement in BCVA from baseline at week 26 was 24.5 percentage points higher with DEX 700 than with sham (P < 0.001).

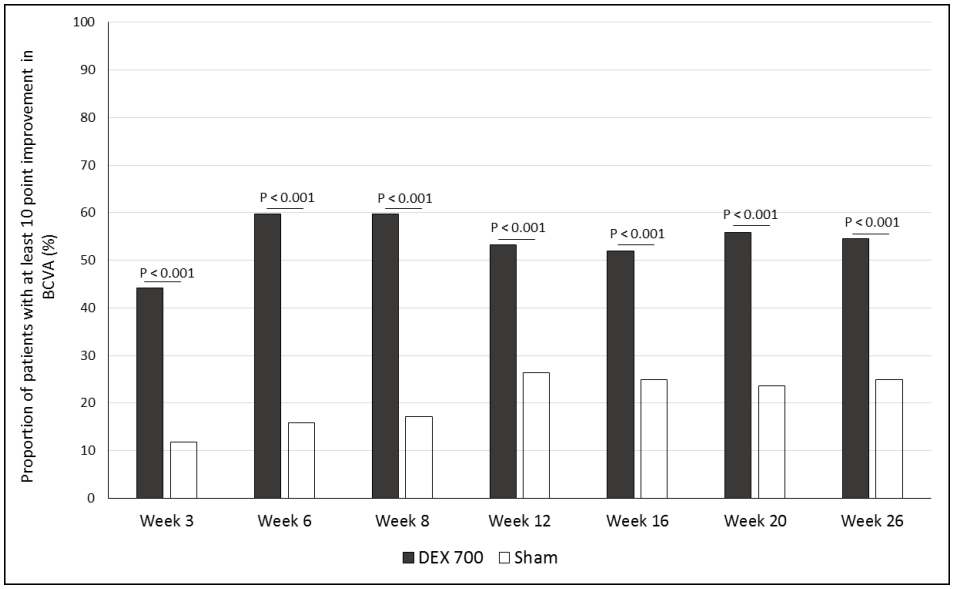
Figure 3 Proportion of patients with ≥ 15 letters improvement in BCVA from baseline in the HURON study (ITT population)



2.4.2.3.2 Improvement of ≥ 10 letters from baseline

At each visit, the proportion of patients with ≥10 letters (equivalent to 0.2 logMAR) improvement in BCVA from baseline was significantly higher with DEX 700 than with sham (P < 0.001). The proportion of patients demonstrating an improvement of ≥ 10 letters from baseline BCVA was nearly twice to more than three times higher with DEX 700 than with sham (Figure 4).

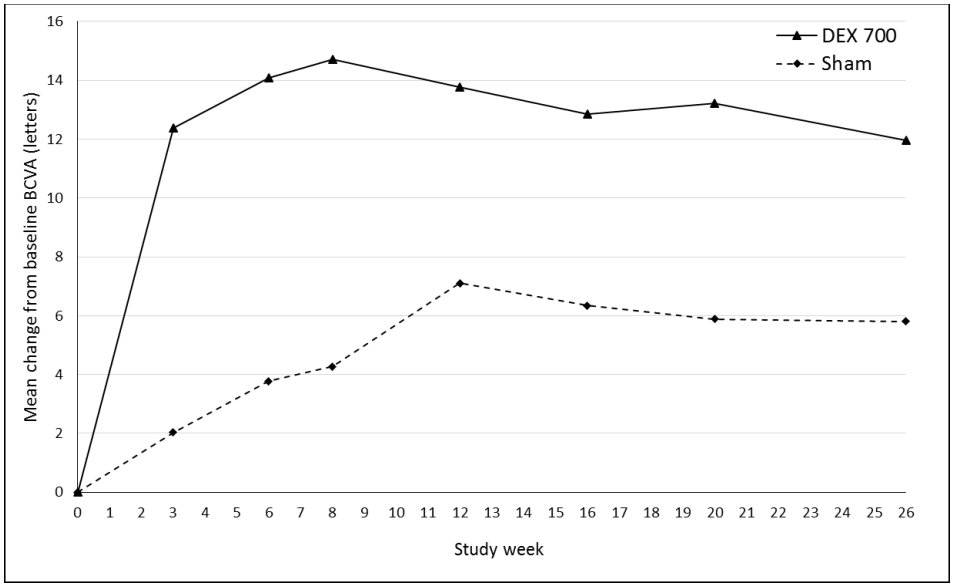
Figure 4 Proportion of patients with ≥ 10 letters improvement in BCVA from baseline in the HURON study (ITT population)



2.4.2.3.3 Mean improvement from baseline

The mean improvement in BCVA from baseline was also significantly greater in the DEX groups than in the sham group throughout the study period (Figure 5) (34). This difference was statistically significant at all points for the DEX 700 group ($P \leq 0.002$) and at all points except week 26 for the DEX 350 group ($P \leq 0.010$).

Figure 5 Mean improvement in BCVA from baseline in the HURON study



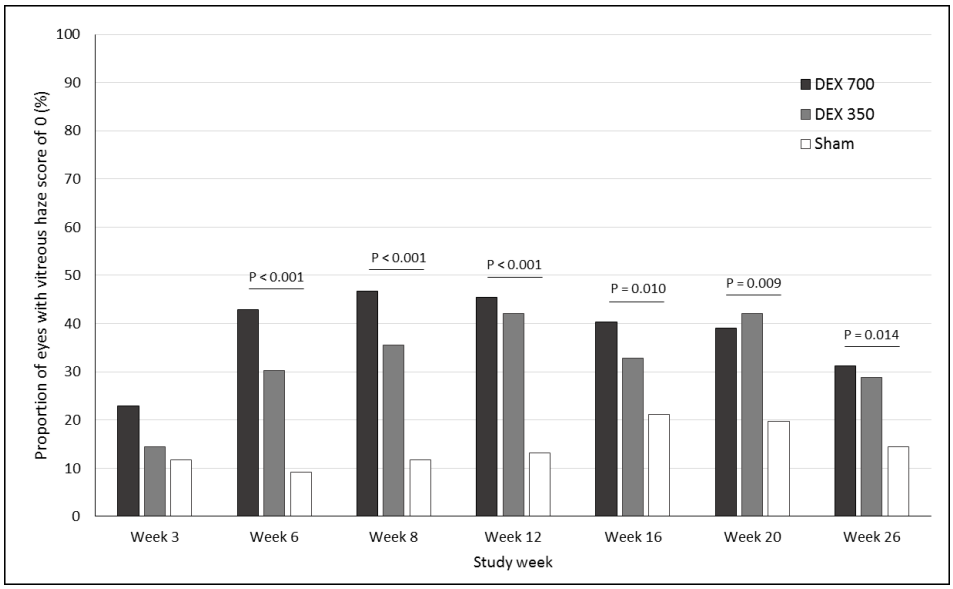
P < 0.001 at all time points except week 26 (P = 0.002).
Source: Lowder et al (2011) (34).

2.4.2.4 Vitreous haze

2.4.2.4.1 Proportion of patients with vitreous haze score 0 (primary efficacy outcome)

At baseline the mean vitreous haze score was approximately +2 in all treatment groups (DEX 700, +2.06; DEX 350, +2.12; sham, +2.01). The proportion of eyes with vitreous haze score 0 at week 8 (the primary time point) was significantly greater in both the DEX 700 group (47%; 36 of 77 patients; P < 0.001) and the DEX 350 group (36%; 27 of 76 patients; P < 0.001) compared with the sham group (12%; 9 of 76 patients) (Figure 6). The proportion of eyes with vitreous haze score 0 was also statistically significantly greater in both the DEX 700 and DEX 350 treatment groups compared with the sham group by week 6, and remained consistently higher until week 26. In the DEX 700 group, the proportion of eyes with vitreous haze score 0 peaked at week 8 (4-fold greater than the proportion in the sham group) and remained twice as high as in the sham group at week 26. Response rates were numerically higher with DEX 700 than with DEX 350 at each visit (except week 20). At week 28, the proportion of patients with vitreous haze score 0 was 16.7% higher than sham in the DEX 700 group, and 14.5% greater than with sham in the DEX 350 group. There were no significant differences between the DEX 700 and DEX 350 groups at any visit.

Figure 6 Proportion of eyes with a mean vitreous haze score 0 in the HURON study (ITT population)



P Values (DEX 700 vs sham) are based on Pearson's chi-square or Fisher's exact test.

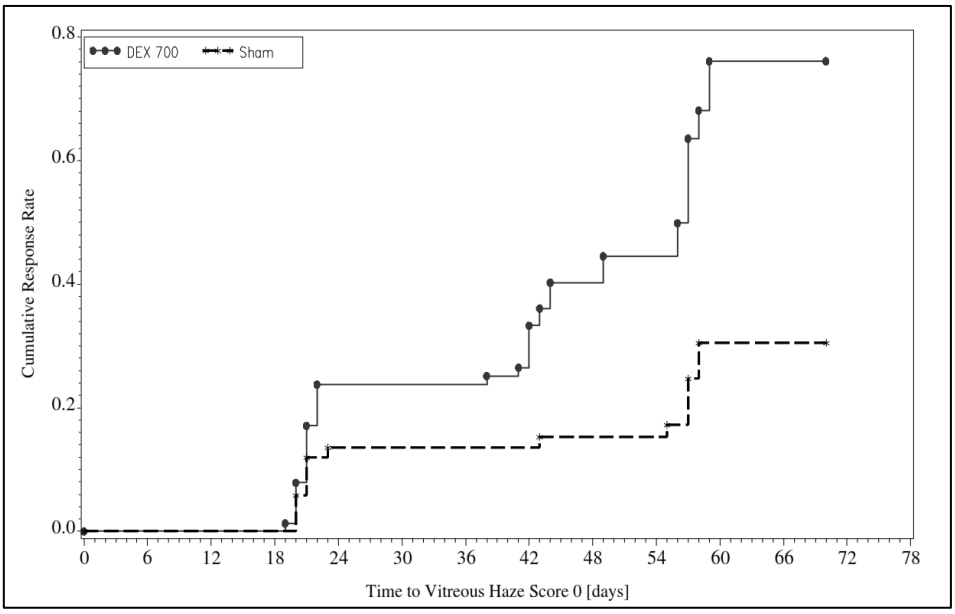
2.4.2.4.2 Time to vitreous haze score 0 (secondary efficacy outcome)

The time to vitreous haze score 0 was calculated from day 0 to the first occurrence of vitreous haze score 0 using the three common scheduled visits of weeks 3, 6 and 8 or unscheduled or early exit visits occurring before week 8. For patients who did not achieve a score of 0, the time to event was censored at the last exam performed among these visits.

Patients receiving DEX demonstrated an earlier onset and greater response, as shown in Figure 7. The cumulative response rate curves were significantly different between the DEX 700 and sham groups (P < 0.001) and between the DEX 350 and sham groups (P = 0.026). Cumulative response rates were consistently higher following DEX treatment than after sham, with separation of the curves as early as week 3 and no crossover during the initial 8 weeks of the study. The cumulative

response rates were also higher with DEX 700 than with DEX 350, with the difference approaching statistical significance (P = 0.052).

Figure 7 Time to vitreous haze score 0 up to week 8 in the HURON study (ITT population)

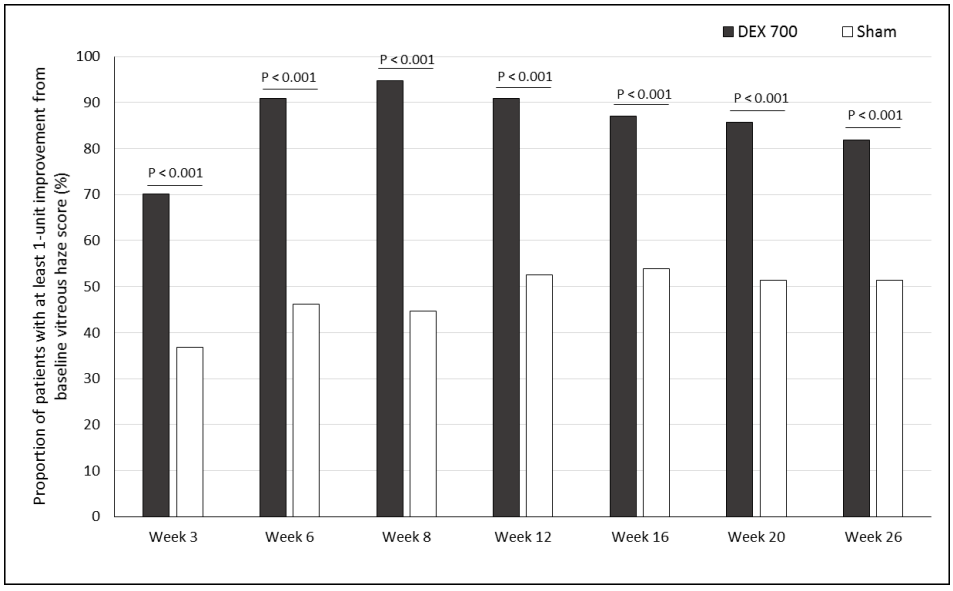


P < 0.001 at all time points.

2.4.2.4.3 Improvement of ≥ 1 unit in vitreous haze score

Ninety-five percent of patients in the DEX 700 group had an improvement of ≥ 1 unit in the vitreous haze score from baseline at the primary time point (week 8), which was 2-fold higher than with sham. The proportion of patients reaching this endpoint was significantly higher with DEX 700 than with sham throughout the 26-week study period (P < 0.001).

Figure 8 Proportion of patients with ≥ 1 unit improvement from baseline in vitreous haze score in the HURON study (ITT population)

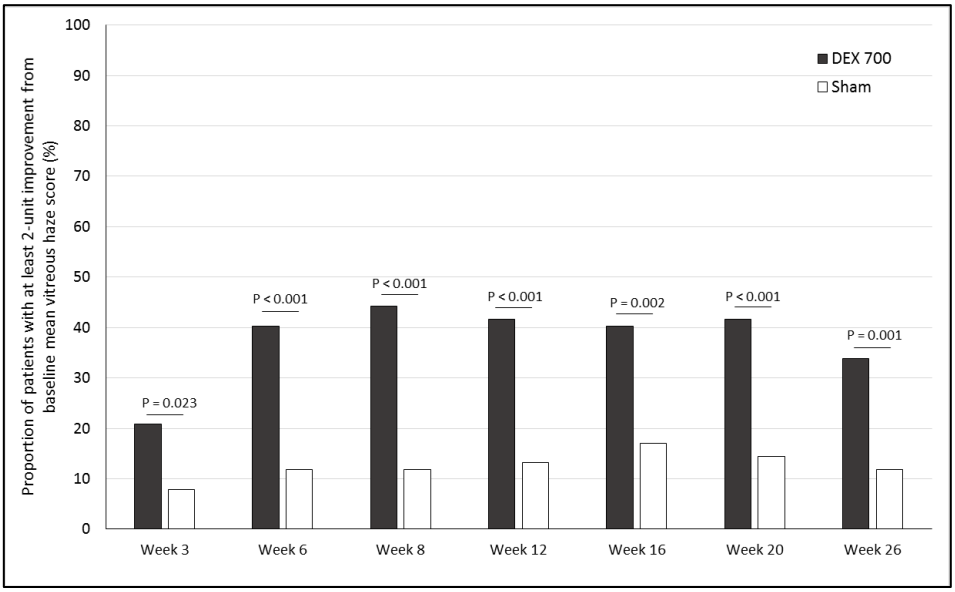


P values (DEX 700 vs sham) are based on Pearson's chi-square or Fisher's exact test.

2.4.2.4.4 Improvement of ≥ 2 units in vitreous haze score

The proportion of patients with an improvement in the vitreous haze score of ≥ 2 units from baseline was significantly higher with DEX 700 than with sham at week 3 (P = 0.023) and at weeks 6–26 (P ≤ 0.002) (Figure 9). The response in the DEX 700 group peaked at week 8 (44.2%) and was maintained up to week 26 (33.8%). The proportion of patients with ≥ 2 unit improvement was significantly higher with DEX 350 than with sham at week 3 (P = 0.034) and weeks 6–26 (P ≤ 0.003). Improvement rates were numerically higher with DEX 700 than with DEX 350 at each visit except week 12.

Figure 9 Proportion of patients with ≥ 2 units improvement in vitreous haze score from baseline in the HURON study (ITT population)



2.4.2.5 Central retinal thickness

CRT was assessed at selected sites using OCT. At baseline, the mean (SD) thickness was 344.0 (141.6) µm in the DEX 700 group and 324.6 (145.5) µm in the sham group. CRT at weeks 8 and 26 was significantly lower than at baseline in both DEX implant groups P ≤ 0.004) whereas changes in the sham group were not significantly different from baseline (P ≥ 0.092). The mean decrease from baseline in CRT was significantly greater with DEX 700 than with sham at week 8 (99.4 [SD 151.8] vs 12.4 [123.7] µm; P ≤ 0.004) but not at week 26 (50.2 [102.9] vs 35.5 [134.9] µm; P ≥ 0.227).

2.4.2.6 Use of rescue medications

Rescue medications were defined as intravitreal/periocular injections of corticosteroids in the study eye or systemic medications (e.g. oral/intravenous corticosteroids or immunosuppressants) taken for uveitis or ocular inflammation which were newly started or increased in dose from treatment day 0.

Use of rescue medications was higher in patients receiving sham than in those treated with DEX throughout the study (Table 9). At the first study visit (week 3), 15% of eyes in the same group required rescue medication, compared with 1% in the DEX 700 group (P = 0.002). The corresponding proportions at week 26 were 38% and 22%, respectively (P = 0.030).

Table 9 Use of rescue medication in the HURON study (ITT population)

From baseline to visit	DEX 700 (n = 77)[a]	Sham (n = 76)[a]	P value[b]
Week 3	1.3%	14.5%	0.002
Week 6	5.2%	18.4%	0.011
Week 8	7.8%	22.4%	0.012
Week 12	14.3%	28.9%	0.027
Week 16	19.5%	32.9%	0.059
Week 20	19.5%	35.5%	0.026
Week 26	22.1%	38.2%	0.030

[a]n values are number of patients
[b]P values based on Pearson's chi-square or Fisher's exact test, DEX 700 vs sham.

2.4.2.7 HRQL

DEX 700 provided significant improvements in vision-related HRQL compared with sham within 8 weeks across many of the VFQ-25 subscales. These improvements were sustained for up to 26 weeks.

Responses to individual items on the VFQ-25 were converted to scores from 0 to 100 according to the developer's scoring manual, with a higher score representing better functionality. The score for each subscale is the average across multiple items within the subscale. The overall composite score is the average of all 11 vision-targeted subscale scores, excluding the general health score.

2.4.2.7.1 Baseline VFQ-25 scores

Significant differences were found between DEX 700 and sham groups at baseline for overall composite score (P = 0.013), colour vision (P = 0.036), dependency (P = 0.008), social functioning (P = 0.014), and mental health (P = 0.012). No significant differences were observed in the other seven VFQ-25 subscale scores. For each subscale with significant differences in mean baseline VFQ-25 scores between the treatment groups, vision-related functioning scores were better in the sham group (Table 10).

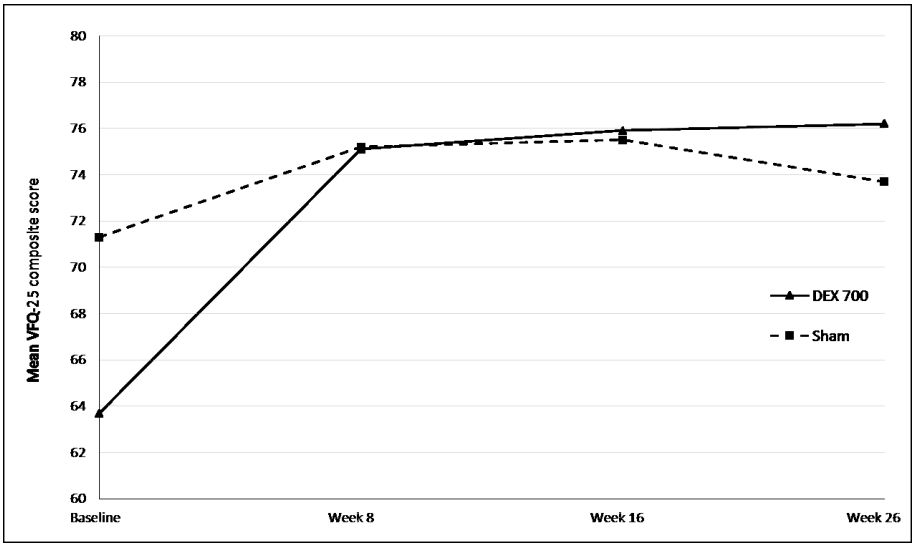
Table 10 Distribution of VFQ-25 scores at baseline in the HURON study (ITT population with baseline and at least one follow-up measurement)

Subscale/total score	N	Unadjusted mean	Standard deviation
Near vision			
DEX 700	73	61.1	25.84
Sham	73	66.1	26.44
Distance vision			
DEX 700	73	66	25.37
Sham	73	69.7	25.3
General health			
DEX 700	73	52.1	23.85
Sham	73	53.1	26.33
General vision			
DEX 700	73	54.2	19
Sham	73	59.2	16.81
Driving			
DEX 700	37	67.2	22.7
Sham	47	71	20.87
Peripheral vision			
DEX 700	73	65.1	28.18
Sham	73	71.9	28.55
Colour vision			
DEX 700	73	81.5	25.69
Sham	73	89	20.83
Ocular pain			
DEX 700	73	65.2	23.03
Sham	73	72.1	25.47
Role difficulties			
DEX 700	73	54.5	28.97
Sham	73	63.5	25.83
Dependency			
DEX 700	73	68.2	32.23
Sham	73	80.5	26.25
Social functioning			
DEX 700	72	75	25.35
Sham	73	84.2	21.15
Mental health			
DEX 700	73	46.9	28.05
Sham	73	58.4	25.07
Overall score			
DEX 700	73	63.7	20.74
Sham	73	71.3	18.98

2.4.2.7.2 Mean change from baseline in VFQ-25 score

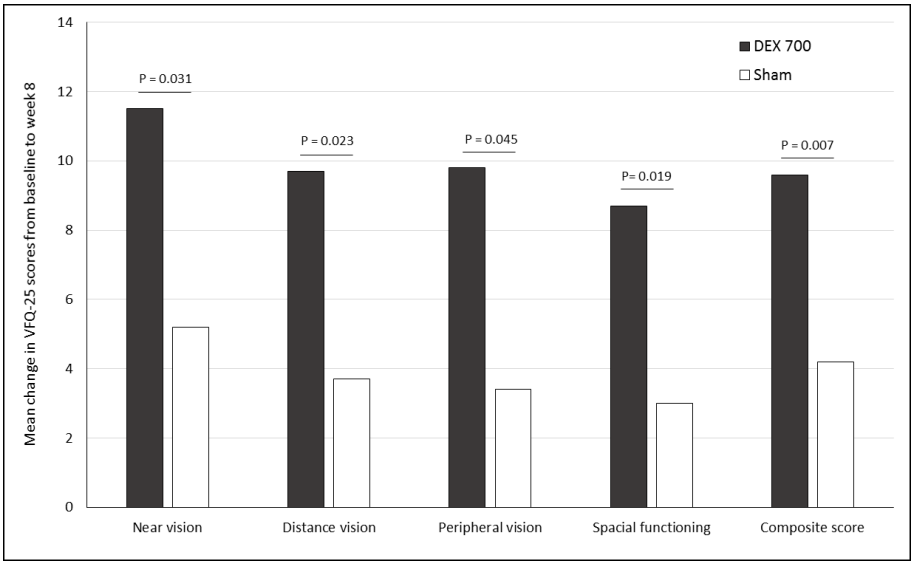
There were no significant between-group differences in the mean raw scores for any of the 11 VFQ-25 subscales, general health item or composite score at weeks 8, 16, and 26/early exit. At the primary time point (week 8), the mean improvement in the overall composite score was 11.62 with DEX 700, compared with 3.42 with sham ($P < 0.001$). The overall composite score increased from baseline to week 16 in both the DEX 700 and sham groups and from week 16 to week 26 with DEX 700, but decreased from week 16 to 26 in the sham group (Figure 10).

Figure 10 Mean unadjusted VFQ-25 composite score by treatment group in the HURON study (ITT population)



For the ANCOVA models with LOCF, there were statistically significant differences between the DEX 700 and sham groups in the change from baseline to week 8 in the overall composite ($P = 0.007$), near vision ($P = 0.031$), distance vision ($P = 0.023$), peripheral vision ($P = 0.045$), and vision-specific social functioning scores ($P = 0.019$) (Figure 11). Improvements in overall composite scores were 9.6 points in the DEX 700 group, compared with 4.2 points in the sham group.

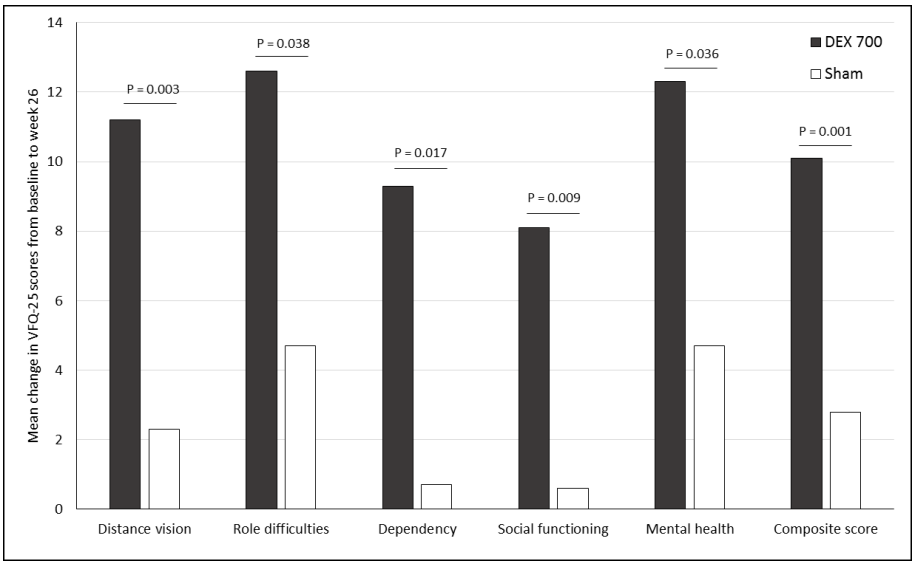
Figure 11 Change in VFQ-25 scores from baseline to week 8 in the HURON study (ITT population)



Values are least mean square change from baseline to week 8.

Statistically significant differences were also seen between the two groups at 26 weeks for changes from baseline in the overall composite (P = 0.001), distance vision (P = 0.003), vision-specific role difficulties (P = 0.038), vision-specific dependency (P = 0.017), vision-specific social functioning (P = 0.009) and vision-specific mental health scores (P = 0.036) (Figure 12). The improvements in overall composite scores were maintained at 26 weeks in the DEX 700 group, with patients reporting a mean improvement of 10.1 points, compared with 2.8 points in the sham group.

Figure 12 Change in VFQ-25 scores from baseline to week 26 in the HURON study (ITT population)



Values are least mean square change from baseline to week 8

2.4.2.7.3 Proportion of patients with ≥ 5-point improvement in VFQ-25 score

By 8 weeks, significantly more patients in the DEX 700 group than in the sham group reported ≥ 5 point improvements in the overall composite score (54.8% vs 27.0%; P < 0.001) (33). This difference was maintained to week 26. Significant differences between the two groups at week 8 were also seen for the proportion of patients with ≥ 5 point in near vision (P < 0.001), distance vision (P = 0.016), general vision (P = 0.003), peripheral vision (P = 0.041), colour vision (P = 0.001), ocular pain (P = 0.002), vision-specific role difficulties (P = 0.039), dependency (P = 0.007), vision-specific social functioning (P = 0.001), and mental health (P = 0.026). These differences generally persisted over the course of the study (Table 11, Figure 13).

Table 11 Proportion of patients with ≥ 5 point improvement in VFQ-25 scores at weeks 8 and 26 in the HURON study (ITT population)

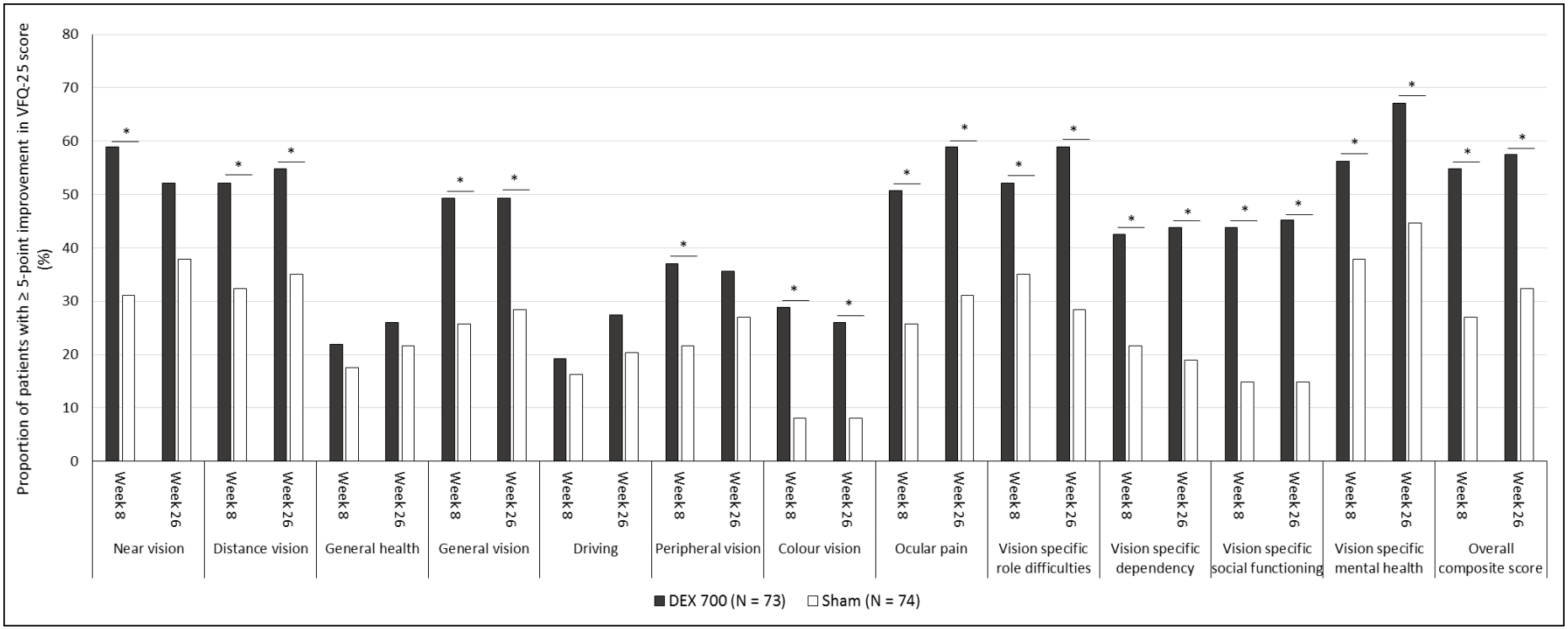
Subscale	Week	DEX 700 (n = 73)	Sham (n = 74)
Near vision	8	58.9 (43)*	31.1 (23)
	26	52.1 (28)	37.8 (28)
Distance vision	8	52.1 (38)*	32.4 (24)
	26	54.8 (40)*	35.1 (26)
General health	8	21.9 (16)	17.6 (13)
	26	26.0 (19)	21.6 (16)
General vision	8	49.3 (36)*	25.7 (19)
	26	49.3 (36)*	28.4 (21)
Driving	8	19.2 (14)	16.2 (12)
	26	27.4 (20)	20.3 (15)
Peripheral vision	8	37.0 (27)*	21.6 (16)
	26	35.6 (26)	27.0 (20)
Colour vision	8	28.8 (21)*	8.1 (6)
	26	26.0 (19)*	8.1 (6)
Ocular pain	8	50.7 (37)*	25.7 (19)
	26	58.9 (43)*	31.1 (23)
Vision-specific role difficulties	8	52.1 (38)*	35.1 (26)
	26	58.9 (43)*	28.4 (21)
Vision-specific dependency	8	42.5 (31)*	21.6 (16)
	26	43.8 (32)*	18.9 (14)
Vision-specific social functioning	8	43.8 (32)*	14.9 (11)
	26	45.2 (33)*	14.9 (11)
Vision-specific mental health	8	56.2 (41)*	37.8 (28)
	26	67.1 (49)*	44.6 (33)
Overall composite score	8	54.8 (40)*	27.0 (20)
	26	57.5 (42)*	32.4 (24)

Values are n (%).

*Significant difference between DEX 700 and sham groups ($P < 0.05$ Pearson chi-squared test).

Source: Lightman et al (2013) (33).

Figure 13 Proportion of patients with ≥5 point improvement in VFQ-25 scores at weeks 8 and 26 in the HURON study (ITT population)



*Significant difference between DEX 700 and sham groups (P < 0.05; Pearson chi-squared test).
Source: Lightman et al (2013) (33).

2.4.2.7.4 Proportion of patients with ≥ 10 point improvements in VFQ-25 score

Similar patterns for significant differences between the DEX 700 and sham groups were seen in the proportions of patients with ≥ 10 point improvements for VFQ-25 scores (33). After 8 weeks, significantly more patients in the DEX 700 group than in the sham group reported ≥ 10 point improvement in the overall composite score (45.2% vs 14.9%; $P < 0.001$). Significant between-group differences were also observed at week 8 for distance vision, general vision, peripheral vision, colour vision, ocular pain, vision-specific role difficulties, vision-specific dependency, vision-specific social functioning, and vision-specific mental health (all $P < 0.05$). In general, these differences were maintained over the course of the study, and at week 26 between-group differences were maintained at week 26 for the composite score and all subscales except for driving and peripheral vision.

2.4.2.8 SF-36 health survey

There were no statistically significant differences between treatment groups at baseline in the mean raw scores for any of the eight subscales, two component summary scores, or the single question to assess patients' perceptions of their present health compared with 1 year ago (Table 12) (10).

Table 12 Mean SF-36 component scores at baseline in the HURON study (10)

SF-36 item (n = 138)	Score, mean (SD)
Physical component summary	47.7 (12.2)
Mental component summary	47.6 (12.7)
Physical functioning	79.7 (23.8)
Role-physical	65.5 (40.7)
Bodily pain	71.3 (23.3)
General health	64.7 (21.5)
Vitality	57.8 (22.5)
Social functioning	82.3 (25.3)
Role-emotional (n = 137)	74.7 (39.5)
Mental health	72.3 (19.0)

2.4.2.9 EQ-5D

There were no significant between-group differences at baseline for any of the self-reported descriptions of health problems on the five dimensions of the EQ-5D.

The mean VAS score at baseline was 67.1 (range 4–100) in the DEX 700 group and 71.0 (3–100) in the sham group. There was no statistically significant between-group difference.

The mean (SD) EQ-5D index value reported by Naik and colleagues (2013) was 0.84 (0.13) using the US valuation tariff (10). Applying the UK tariff, the mean EQ-5D index value at baseline was 0.77 (0.21) in the DEX 700 group and 0.80 (0.22) in the sham group.

The EQ-5D health questionnaire was not administered during follow-up because it does not contain vision-specific items.

2.4.3 Conclusions from HURON

HURON is the pivotal phase III trial that provided data to support the marketing authorisation of DEX 700 for the treatment of non-infectious uveitis. DEX 700 demonstrated rapid, substantial and sustained efficacy compared with sham treatment in patients with non-infectious intermediate or posterior uveitis. Benefits included improvement in BCVA, vitreous haze score and CRT, which were seen by 3 weeks post-implantation and were maintained until the end of follow-up (26 weeks post-implantation). The efficacy of DEX 700 was supported by statistically significant and clinically meaningful improvements in vision-related HRQL, demonstrated by improvements in multiple VFQ-25 subscales and the composite score.

2.5 Supporting efficacy evidence from RCTs

A phase II dose-ranging study with DEX PS DDS was conducted in a broader population, including patients with persistent macular oedema associated with diabetic retinopathy, uveitis, RVO or Irvine–Gass syndrome (DC103-06; NCT00035906). This study included a subgroup of only 14 patients with uveitis. These data were presented to the EMA as part of the application for the licence extension for the uveitis indication but were not discussed further given the small number of patients with uveitis (26).

2.5.1 Other RCTs by independent sponsors

No other RCTs of DEX 700 for the treatment of uveitis were identified. A search of clinical trials.gov identified two RCTs involving DEX 700 for the treatment of uveitic macular oedema. However, recruitment is ongoing and they are not scheduled to complete until at least 2018 (NCT02374060 and NCT02623426).

2.6 Efficacy from non-randomised studies

DEX 700 is the only treatment available for posterior segment uveitis to be supported by systematically collected real-world evidence. The efficacy results of HURON, including the impact on VA, are supported by the results of real-world studies reporting the effectiveness of DEX 700 in routine clinical practice in several countries. Real-world studies have also demonstrated the clinical effectiveness of DEX 700 in a more diverse range of patients than was included in the HURON trial. This evidence is discussed in the following sections.

2.6.1 Tomkins-Netzer *et al.,* 2014: Retrospective review of patients undergoing treatment and re-treatment with DEX 700 for non-infectious uveitis in UK clinical practice at two treatment centres

This is the largest UK-specific cohort of patients with non-infectious uveitis treated with DEX 700. The study included a follow-up period of up to 24 months (mean 17.3 months).

This study demonstrated that DEX 700 reduces ocular inflammation and improves long-term visual function, with a manageable safety profile. The benefits were shown to be cumulative, and patients showed continued improvements in visual function after several implantations. Notably, 58% of the study population had a baseline vitreous haze score 0, which would have made them ineligible for

the HURON trial. This study can therefore be considered to demonstrate clinical effectiveness in a broader patient population than that included in HURON.

2.6.1.1 Study design and baseline characteristics

This retrospective study was conducted at Moorfields Eye Hospital in London and the Royal Surrey County Hospital in Guildford and included all patients with non-infectious uveitis seen from the start of 2008 to the end of 2013 who received DEX 700 (35). The study included 38 eyes of 27 patients (11 men, 16 women). Data were collected on the day of implantation and at months 1, 2, 3, 6, 12 and 24 (depending on the length of follow-up).

One patient was lost to follow-up immediately after implantation and was not included in any further analyses. Mean follow-up was 17.3 (SEM 1.8) months after the first implant, and 11 eyes had more than 24 months' follow-up. Fourteen eyes (36.9%) received a single implant and 24 eyes (63.1%) had multiple implantations. Baseline characteristics are presented in Table 13.

Table 13 Demographic and baseline characteristics in the study of Tomkins-Netzer *et al.* (2014) (35)

Characteristic	
Age, years, mean (SEM)	48 (2.2)
Female (n, %)	16 (42.1)
Diagnosis (n, %)	
Intermediate uveitis	9 (23.69)
Posterior uveitis plus panuveitis	29 (76.31)
Reason for treatment (n, %)	
Cystoid macular oedema	35 (92.1)
Vitritis	3 (7.89)
Baseline visual acuity, logMAR, mean (SEM)	0.47 (0.05) (Snellen equivalent 20/60)
Baseline vitreous haze severity (n, %)	
Score of 0	22 (57.89)
Score of +0.5 to +2	16 (42.11)
Baseline CRT, µm, mean (SEM)	453.29 (33.57)
Baseline IOP, mmHg, mean (SEM)	13.870.43)
Phakic lens at baseline (n, %)	21 (55.26)
Steroid responders at baseline (n, %)	7 (18.42)
Repeat implants (n, %)	
2	14 (36.9)
3	7 (18.4)
4	2 (5.2)
6	1 (2.6)

2.6.1.2 BCVA

Mean BCVA improved significantly from baseline at first implantation, from 0.47 (SEM 0.05) logMAR (Snellen equivalent 20/60) to 0.27 (0.07) logMAR (20/37) at 2 months ($P < 0.001$) but deteriorated to 0.43 (0.12) logMAR (20/54) by 6 months.

2.6.1.3 Central retinal thickness

Mean (SEM) CRT decreased significantly from 453 (SEM 34) μm at baseline to 263 (44) μm at 1 month after first implantation (P = 0.003). Macular oedema persisted in 50% of eyes, but the remaining eyes demonstrated a decrease in in CRT of 127 (52) μm at 6 months (P = 0.01); improvement was maintained until 12 months post-implantation.

2.6.1.4 Vitreous haze

There was a statistically significant improvement in the proportion of eyes achieving vitreous haze score 0 following the first implantation, from 58% at baseline to 83% at 1 month (P = 0.03), which remained until month 6 (85%, P = 0.02) but had decreased by 12 months (53%).

2.6.1.5 Repeat implantations

Repeat implantations were administered to 24 eyes and were associated with similar clinical responses to those achieved after first implantation.

After second implantation, BCVA improved from 0.55 (0.1) logMAR (Snellen equivalent 20/70) to 0.22 (0.07) logMAR (20/33) at 1 month (P = 0.004). BCVA decreased after 1 month but remained above baseline until the end of follow-up. A similar trend was observed after third implantation, although the improvements were not statistically significant. Three eyes received a fourth implant, which resulted in improvement of BCVA from 0.83 (0.17) logMAR (20/135) at baseline to 0.32 (0.09) logMAR (20/42) within 1 month. One eye received two further implants, which also resulted in improved BCVA within 1 month.

CRT decreased by 187 (52.9) μm at 2 months after second implantation (P = 0.043). Improvement in CRT was also observed after third implantation, although the improvement was not statistically significant, and after fourth implantation (decrease of 225.67 [109.85] μm at 1 month).

There was a trend towards an improvement in the proportion achieving vitreous haze score 0 after second implant, although this did not reach statistical significance (72.7% at baseline to 91.7% at 1 month); a similar trend was observed following a third implant.

2.6.1.6 Duration of effect

The median time to relapse was 6 months (range 2–42 months) after first implantation, and relapse occurred in 69% of eyes. After the second implants, the median time to relapse was also 6 months (range 1–12 months), and relapse occurred in 48% of eyes. The time to relapse after first and second implant was similar (P = 0.29).

2.6.1.7 Long-term treatment effect

After the first implant, systemic or local immunosuppressive treatment was reduced or stopped in 33 eyes of 21 (78%) patients. The long-term cumulative effect of treatment with dexamethasone implants was examined in these eyes. Mean follow-up was 17.81 (SEM 2.1) months. Repeated dexamethasone implants resulted in a continued improvement in BCVA and a significant improvement in CRT and then stabilisation.

2.6.1.8 Bilateral implantation

Eleven patients received bilateral dexamethasone implants; the second implant was administered 113 ± 32 days after the first. In three patients there was also a response in the second eye, with reduction in CRT and improvement in BCVA. Four of the 11 patients received systemic corticosteroids and immunosuppressive agents at baseline, the doses of which were tapered after the second eye was treated, within 12 ± 3days.

2.6.2 Zarranz-Ventura *et al.,* 2014: Multicentre retrospective review of patients treated with DEX 700 for non-infectious uveitis in UK and Spanish clinical practice

This study is the largest cohort of patients (n=63) for which outcomes are reported following treatment with DEX 700 for non-infectious uveitis, including patients from the UK. More than half (60.9%) of the cohort had posterior or intermediate uveitis. The majority (83.9%) of this study population would not have been included in HURON because baseline vitreous haze scores were < 1.5. DEX 700 provided rapid and sustained clinical benefit, allowing reduction in the dose of systemic corticosteroid or immunosuppressive therapies. This therefore underlines the clinical effectiveness of DEX 700 in a much broader population than was included in HURON.

2.6.2.1 Study design and baseline characteristics

This was a multicentre retrospective study that included patients receiving DEX 700 for non-infectious uveitis between October 2010 and July 2013 at four specialist centres, two in the UK and two in Spain (15). Data were collected at baseline and at months 1, 3, 6, and 12 following first implantation. The study included 142 implants in 82 eyes of 63 patients, including those with a diagnoses of panuveitis, anterior chronic uveitis, acute anterior uveitis, and retinal vasculitis (39% of the study population). Nineteen patients (30.1%) received bilateral implantation. Population demographics and baseline characteristics are presented in Table 14.

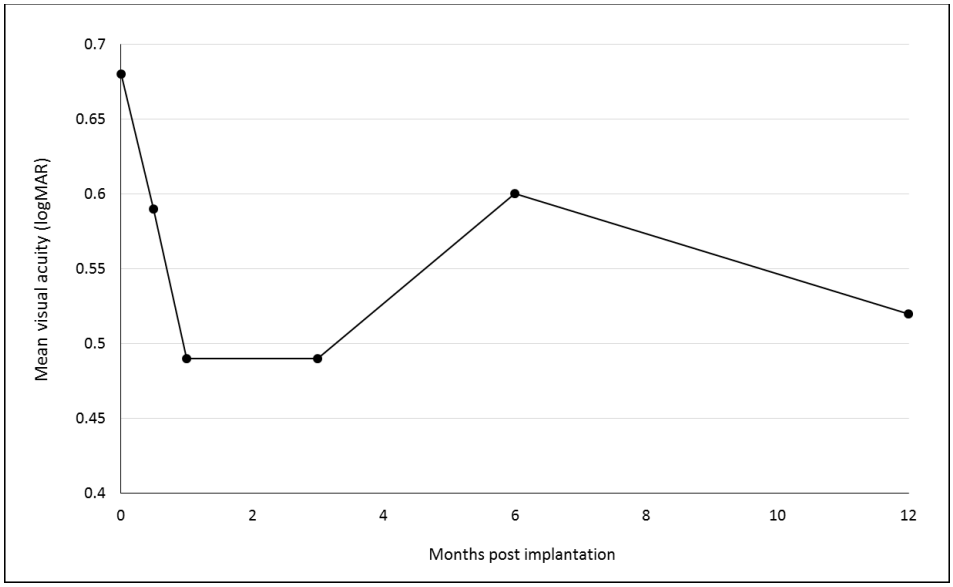
Table 14 Patient demographics and baseline characteristics in the study by Zarranz-Ventura *et al.* (2014) (15)

Characteristic	
Age, years, mean (SD)	47.4 (17.2)
Female (%)	74.1
Uveitis anatomical classification (%)	
Intermediate uveitis	37.8
Posterior uveitis	23.1
Panuveitis	21.9
Anterior chronic uveitis	13.4
Acute anterior uveitis	2.4
Retinal vasculitis	1.2
Indication (%)	
Cystoid macular oedema	61
Vitritis	28
Cystoid macular oedema + vitritis	11
Mean visual acuity at baseline	
logMAR, mean (SD)	0.68 (0.47)
Snellen equivalent	20/90
Vitreous haze score at baseline (%)	
0	48.6
0.5	11.8
+1	23.6
+2	11.8
Score of +3	2.6
Score of +4	1.3
Mean (SD) CRT at baseline, µm	462 (190)
Mean (SD) IOP at baseline, mmHg	14.1 (4.0)
Baseline systemic therapies (%)	53.9
Local therapies (%)	63.4

2.6.2.2 Visual acuity

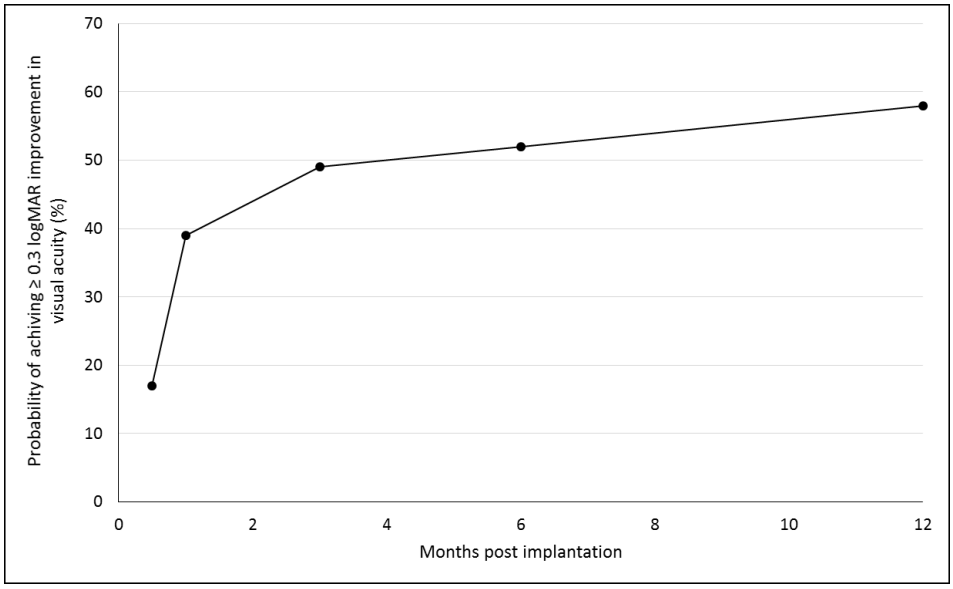
Mean VA was 0.68 (SD 0.4) logMAR (Snellen equivalent 20/90) at baseline, improving to 0.59 (0.4) logMAR (20/78) at 2 weeks post-injection, 0.49 (0.4) logMAR (20/62) at 1 month, 0.49 (0.5) logMAR (20/62) at 3 months, 0.60 (0.5) logMAR (20/80) at 6 months, and 0.52 (0.5) logMAR (20/66) at 12 months ($P < 0.01$ at each point) (Figure 14). The probability of VA improvement ≥ 0.3 logMAR units was 17% at 2 weeks, 39% at 1 month, 49% at 3 months, and 52% at 6 months, which was maintained at 12 months (58%) (Table 15). The median time to improvement in VA ≥ 0.3 logMAR units was 6 months (95% CI 5.34–7.79).

Figure 14 Mean BCVA 0–12 months post-implantation (Zarranz-Ventura *et al.*, 2014) (15)



Improvement from baseline $P < 0.01$ at each time point.

Figure 15 Probability of visual acuity improvement ≥ 0.3 logMAR units up to 12 months after implantation (Zarranz-Ventura et al 2014) (15)



2.6.2.3 Central retinal thickness

CRT was only analysed in eyes with cystoid macular oedema (59 eyes). Mean CRT in this cohort was 469 (SD 193) µm at baseline, improving to 326 (81) µm at 2 weeks, 267 (74) µm at 1 month, 318 (149) µm at 3 months, 366 (140) µm at 6 months, and 355 (160) µm at 12 months ($P < 0.01$ at each point).

2.6.2.4 Vitreous haze

Vitreous haze was analysed only in eyes with vitritis at baseline (vitreous haze score ≥ +0.5; 39 eyes). The probability of achieving vitreous haze score improvement (2-step improvement or change from +0.5 to 0) was 41% at 2 weeks, 63% at 1 month, 73% at 3 months, 79% at 6 months and 88% at 12 months. The median time to improvement in the vitreous haze score was 1 month (95% CI 0.6–1.3).

2.6.2.5 Frequency of repeat implantations

The mean number of implantations was 1.7 (SD 0.8), with a median of one implant over a mean follow-up of 15.4 months. Second implants were required in 24 eyes (29.3%), and 15 eyes (18.2%) required three or more implants. The probability of requiring a second implant increased from 26% at 6 months to 47% at 9 months and 51% at 12 months. The median time to second implantation was 10 months (95% CI 6.3–13.6).

2.6.2.6 Concomitant systemic immunosuppressive or corticosteroid treatment

Half (53.9%) of patients (34 of 63) were receiving systemic treatments at baseline:

- 14.3% (9 of 63) were receiving prednisone
- 9.5% (6 of 63) were receiving one second-line immunosuppressive therapy
- 30.1% (19 of 63) were receiving prednisone plus immunosuppressive therapy (20.6% [13 of 63] as dual therapy and 9.5% [6 of 63] as triple therapy).

The probability of dose reduction (defined as ≥ 5 mg prednisone or any reduction in immunosuppressive therapy) was 36% at 1 month, 42% at 3 months, 46% at 6 months, and 62% at 12 months. The probability of systemic steroid discontinuation was 8% at 1 and 3 months, 11% at 6 months, and 36% at 12 months.

2.6.3 Miserocchi *et al*., 2012: Retrospective study of patients treated with DEX 700 for chronic posterior non-infectious uveitis at a single Italian centre

In this small cohort of patients at a single treatment centre in Italy, DEX 700 provided a sustained effect in the treatment of chronic non-infectious posterior or intermediate uveitis.

2.6.3.1 Study design and baseline characteristics

This was a retrospective study of the case records from 12 patients with chronic posterior non-infectious uveitis who received DEX 700 from August 2011 to June 2012 at a single centre in Milan,

Italy (40). The study included 14 affected eyes receiving 15 implants. Demographic and baseline characteristics are presented in Table 15.

Table 15 Demographic and baseline characteristics in the study by Miserocchi *et al.* (2012) (40)

Characteristic	
Age, years, mean (SD)	55.16 (15)
Female (n, %)	8 (66.67)
Location (n, %)	
Intermediate	3 (25)
Posterior	9 (75)
Indication (%)	
Cystoid macular oedema	5 (41.67)
Active choroiditis	2 (16.67)
Cystoid macular oedema + retinal vasculitis	2 (16.67)
Cystoid macular oedema + vitritis	3 (25)
Mean BCVA at baseline	20/80
Mean (SD) CRT at baseline, µm	496 (123)

2.6.3.2 BCVA

The mean BCVA was 20/80 (0.6 logMAR) before implant and 20/40 (0.3 logMAR) at the end of follow-up (6–11 months). The 14 treated eyes showed a mean improvement from baseline in BCVA of 3.3 lines at the end of follow-up (range 0–6 lines). The BCVA results are summarised in Table 16.

Table 16 BCVA results from Miserocchi *et al.* (2012) (40)

Patient	**Baseline BCVA (logMAR)**	**Final BCVA (logMAR)**	**Length of follow-up (months)**
1 (right eye)	20/63 (0.5)	20/25 (0.1)	9
1 (left eye)	20/100 (0.7)	20/63 (0.5)	7
2	20/80 (0.6)	20/20 (0)	11
3 (right eye)	20/63 (0.5)	20/63 (0.5)	11
3 (left eye)	20/40 (0.3)	20/40 (0.3)	9
4	20/80 (0.6)	20/50 (0.4)	8
5	20/100 (0.7)	20/63 (0.5)	6
6	20/50 (0.4)	20/25 (0.1)	10
7	20/80 (0.6)	20/32 (0.2)	9
8	20/125 (0.8)	20/40 (0.3)	8
9	20/200 (1.0)	20/50 (0.4)	9
10	20/125 (0.8)	20/40 (0.3)	10
11	20/80 (0.6)	20/32 (0.2)	9
12	20/50 (0.4)	20/20 (0)	10

2.6.3.3 Central retinal thickness

CRT was 496 (123) µm at baseline and improved to 226 (66) µm by the end of follow-up.

2.6.3.4 Concomitant systemic immunosuppressive or corticosteroid treatment

All the patients in this study were receiving systemic immunosuppressive or corticosteroid treatments for associated autoimmune disease or uveitis. Three patients were able to reduce the daily dose of corticosteroids after receiving DEX 700.

2.6.4 Palla *et al*., 2015: Retrospective review of patients treated with DEX 700 for non-infectious uveitis at a single Indian centre

In a small cohort of patients at a single treatment centre in India, DEX 700 provided a rapid effect in the treatment of non-infectious intermediate uveitis.

2.6.4.1 Study design and baseline characteristics

This retrospective study reviewed the medical records of 15 patients at a single treatment centre in Chennai, India, who had received a DEX 700 for the treatment of non-infectious intermediate uveitis between March 2011 and June 2013 (41). Data were collected at baseline, 6 weeks, 6 months and the last visit within 12 months after implantation. A total of 20 eyes were included in the study. Patient demographics and baseline characteristics are presented in Table 17.

Table 17 Patient demographics and baseline characteristics in the study reported by Palla *et al*. (2015) (41)

Characteristic	
Age, years, mean	39.8
Female (n, %)	7 (46.6)
Mean baseline BCVA, logMAR units (Snellen equivalent)	0.666 (20/93)
Mean CRT at baseline, µm	536.1
Number of phakic eyes at baseline, n (%)	20 (100)
Number of eyes having epiretinal membrane at presentation, n (%)	2 (10)

2.6.4.2 BCVA

Mean BCVA improved from 0.666 logMAR units (Snellen equivalent 20/93) at baseline to 0.479 logMAR units (20/60) at 6 weeks after implant, which was stated as statistically significant but the P value was not reported. The improvement from baseline in mean BCVA was still observed at the last follow-up measurement.

2.6.4.3 Central retinal thickness

Mean CRT improved from 563.1 µm at baseline to 361.4 µm at 6 weeks post-implantation. The trend of improved CRT continued at each follow-up measurement. Two eyes that had epiretinal membrane at baseline demonstrated minimal improvement in CRT through the study.

2.6.4.4 Vitreous haze

The proportion of patients achieving vitreous haze score 0 was 60%, 45%, and 30% at 6 weeks, 6 months, and the last visit, respectively.

2.6.5 Lam *et al.*, 2015 (NCT01805323): Multicentre retrospective chart review of patients treated with DEX 700 for macular oedema in Canadian clinical practice

Lam *et al.* (2015) reported improvements in a range of outcomes in patients treated with DEX 700 within its marketing authorisation for the treatment of non-infectious uveitis affecting the posterior segment of the eye in Canadian clinical practice.

2.6.5.1 Study design and baseline characteristics

This was a multicentre, retrospective, open-label, exploratory chart review of data collected between 1 December 2010 and 1 December 2012 from patients with macular oedema who received one or more DEX 700 implants at ten Canadian retina practices, including one uveitis centre (NCT01805323) (42). All patients had a diagnosis of retinal disease involving macular oedema in the study eye(s), received at least one DEX 700 implant, and had a minimum of 3 months follow-up data (12 ± 2 weeks) after the first injection. Data were collected at baseline and at a follow-up visit 2–26 weeks post-implantation.

The study involved 120 study eyes in 101 patients with diagnoses of DMO, RVO, or uveitis. The location of uveitis was not reported, although but the authors state that, at the time the study was conducted, the implant was approved in Canada for treatment of non-infectious uveitis affecting the posterior segment of the eye. This study has therefore been reviewed with the assumption that the uveitis cohort represents eyes with this condition. The study included 23 eyes from 20 patients within the uveitis cohort; the data for this cohort are presented in Table 18 (demographics) and Table 19 (baseline characteristics).

Table 18 Demographic characteristics in the uveitis cohort of the study reported by Lam *et al.* (2015) (42)

Characteristic (n = 20 patients)	
Age, years, mean	49.8
Female (n, %)	10 (50)
Race, n (%)	
Asian	0 (0)
Black	2 (10)
Hispanic	0 (0)
Other	1 (5)
White	17 (85)

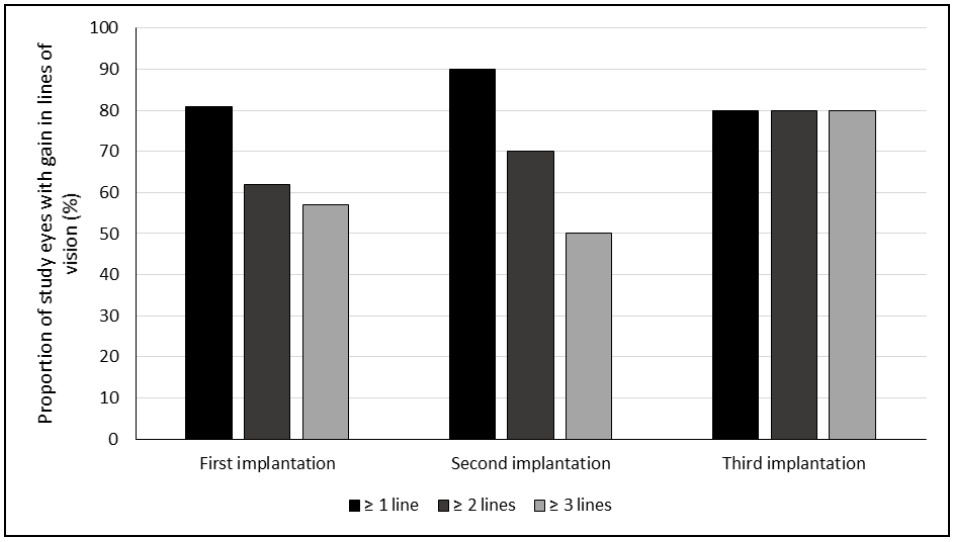
Table 19 Baseline characteristics in the uveitis cohort of the study reported by Lam *et al.* (2015) (42)

Characteristic (n = 23 eyes)	
Visual acuity	
LogMAR, mean ± SE	0.71 ± 0.07
Snellen equivalent	20/102
CRT, mean ± SE (µm)	517.2 (40.3)
IOP, mean ± SE (mmHg)	12.3 ± 0.8
History of steroid response, n (%)	8 (34.8)
Continuing prior IOP-lowering medication, n (%)	5 (21.7)

2.6.5.2 BCVA

Figure 16 shows the proportion of eyes with improved vision after each of three DEX 700 implants. After first implantation, 17 of 21 eyes (81%) gained ≥ 1 line of vision, 13 (62%) gained ≥ 2 lines, and 12 (57%) gained ≥ 3 lines. After second implantation, 9 (90%), 7 (70%), and 5 of 10 eyes (50%) gained ≥ 1, 2, or 3 lines of vision, respectively. Four of 5 eyes (50%) gained ≥ 3 lines of vision after a third implantation.

Figure 16 Proportion of eyes with improved vision after first, second and third implantations reported by Lam *et al.* (2015)



2.6.5.3 Central retinal thickness

Seventeen of 23 eyes with a diagnosis of uveitis at baseline showed improvement in CRT, with a mean peak improvement of 255.6 (SE 43.6) µm. Eyes that had not undergone prior PPV showed a greater mean peak improvement from baseline than eyes that had (295.1 ± 54.0 µm vs 161.0 ± 20.4 µm).

2.6.5.4 Repeat implantations

The mean (± SE) number of implantations for study eyes with uveitis was 1.7 ± 0.2. The mean time from first to second implantations was 4.7 ± 0.3 months, and the mean change from second to third implantation was 3.4 ± 0.4 months.

2.6.6 Nobre-Cardoso *et al.*, 2016: Retrospective review of patients treated with DEX 700 for non-infectious uveitic macular oedema at a single French centre

This study showed a rapid and sustained improvement across a range of outcomes following treatment with DEX 700. The study further demonstrated that the mean time to repeat implantation was similar after first and second implantation, again demonstrating effect beyond the limits of the HURON study.

2.6.6.1 Study design and baseline characteristics

This retrospective non-comparative study included patients with non-infectious uveitis and macular oedema who received their first DEX 700 implant between August 2012 and December 2013 at the Pitié-Salpêtrière Hospital, Paris, France (43). Data were collected before each implantation and at 1, 3, 6, and 12 months post-implantation. The study included 41 eyes from 31 patients. Mean (± SD) follow-up was 13.4 ± 5.9 months after first implantation (median 14 months; range 2–23 months). Demographic and baseline characteristics are presented in Table 20.

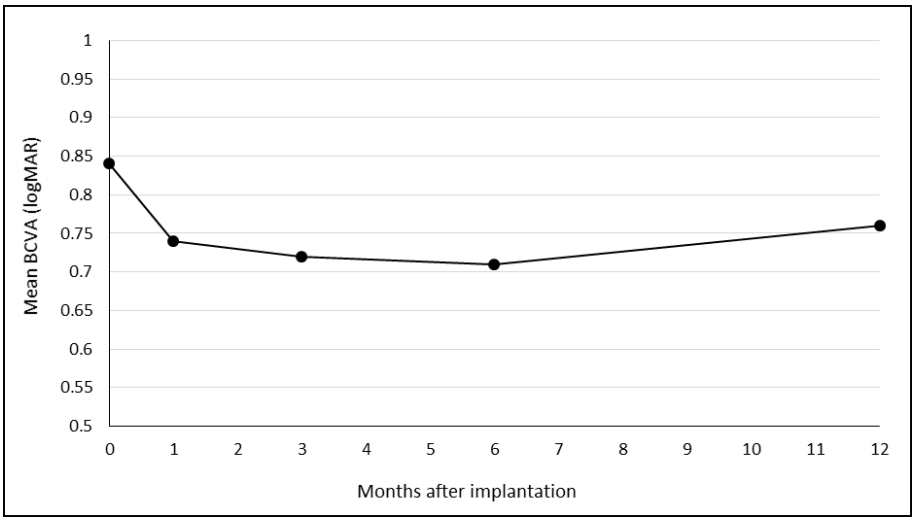
Table 20 Demographic and baseline characteristics in a French study reported by Nobre-Cardoso *et al*. (2016) (43)

Characteristic (n = 31 patients, 41 eyes))	
Age, years, mean ± SD	57.9 ± 13.1
Female (n, %)	22 (71)
Anatomic classification of uveitis, n (%)	
Panuveitis	20 (64.5)
Posterior uveitis	8 (25.8)
Anterior uveitis with macular oedema	2 (6.5)
Intermediate uveitis	1 (3.2)
Baseline BCVA, mean ± SD	
LogMAR	0.84 ± 0.8
Snellen equivalent	20/140 ± 20/130
Baseline vitreous haze score, n (%)	
0	21 (51.2)
+0.5 to +2	20 (48.8)
Baseline CRT, µm, mean ± SD	461.1 ± 158.2
Multiple implantations, n (%)	
2	10 (24.4)
3	2 (4.9)
4	1 (2.4)

2.6.6.2 BCVA

A significant improvement in mean BCVA was achieved at 1 month after first implantation, from 0.84 ± 0.81 logMAR (Snellen equivalent 20/140) at baseline to 0.74 ± 0.84 logMAR (20/110) ($P < 0.01$). Mean BCVA remained below baseline at 12 months post-implantation (Figure 17).

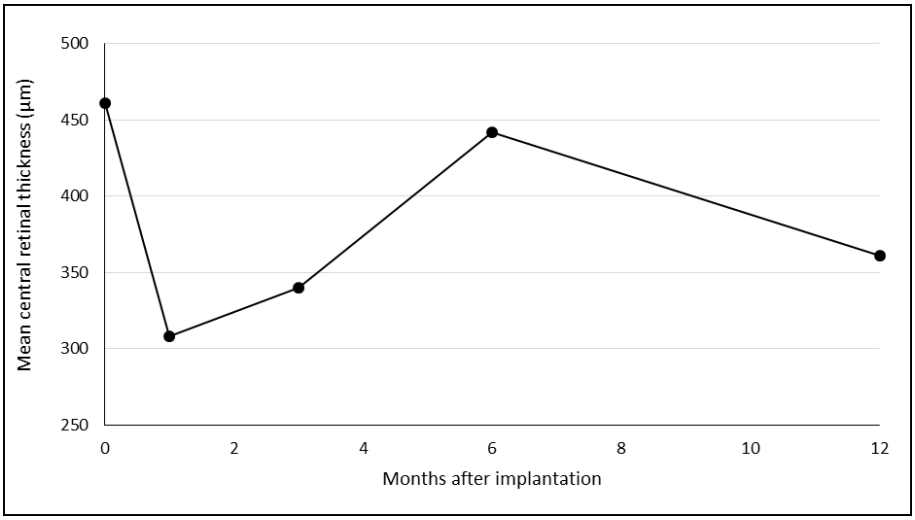
Figure 17 Improvement in mean BCVA following first implantation (Nobre-Cardoso *et al.*, 2016)



2.6.6.3 Central retinal thickness

After first implantation there was a significant improvement in mean CRT, from 461 ± 158 µm at baseline to 308 ± 93 µm at 1 month ($P < 0.001$). At 3 months, macular oedema had relapsed in 31.3% of eyes, with a slight increase in the average CRT to 340 ± 110 µm, although this change was not significant when compared with the value at 1 month. CRT was improved at month 3 compared with baseline ($P < 0.001$). At 6 months, CRT had increased in all but nine eyes compared with month 3 (mean 442 ± 172 µm; $P < 0.001$). A further increase in CRT was observed in three eyes between 6 and 12 months, although the mean CRT decreased. After one implant, six eyes remained free of any relapse in macular oedema at 12 months' follow-up. Figure 18 shows the improvement in CRT following first implantation.

Figure 18 Improvement in mean central retinal thickness following first implantation (Nobre-Cardoso *et al.*, 2016)



2.6.6.4 Vitreous haze

The proportion of patients with vitreous haze score 0 increased from 51.2% at baseline to 71.1% at month 1 ($P < 0.001$), and 75.6% at month 3 ($P < 0.01$). The proportion of eyes with vitreous haze score 0 at month 12 was higher than at baseline (64.7%).

2.6.6.5 Repeat implantations

Mean time to relapse after first implantation (defined as an increase of ≥ 50 µm in CRT from the value at 1 month post-implantation) was 6.7 ± 3.7 months. At 12 months, the overall relapse rate was 83.3%.

In 13 eyes in which there was a relapse after a positive response to the first implant, the mean time to a second implantation was 7.1 ± 2.9 months after first implantation. Repeat implantations improved BCVA (+ 0.08 logMAR) and CRT (304 µm decrease) at 1 month post-implantation.

After repeat implantation, mean time to relapse was 5.0 ± 1.6 months, which was similar to that with first implantation ($P = 0.689$).

2.6.7 Pleyer *et al.*, 2014: Prospective non-comparative case series of patients treated with a single DEX 700 for non-infectious intermediate or posterior uveitis in Germany

Pleyer et al (2014) reported an improvement in cystoid macular oedema that was maintained to 24 weeks of follow-up. Systemic corticosteroid therapies could be reduced or discontinued in 14 of 32 patients (44%).

2.6.7.1 Study design and baseline characteristics

Patients aged ≥ 18 years with vitreous haze and/or macular oedema were enrolled in this prospective non-comparative study. All patients were examined at baseline, 1 day after implantation and at 4, 12, and 24 weeks after implantation (39).

The study included 84 eyes from 84 patients treated at Charité University Medicine Berlin or the Ludwig Maximilian University in Munich. Forty-three patients (51%) had intermediate uveitis and 41 (49%) had posterior uveitis. Demographic and baseline characteristics are presented in Table 21.

Table 21 Demographic and baseline characteristics in the study reported by Pleyer *et al.* (2014) (39)

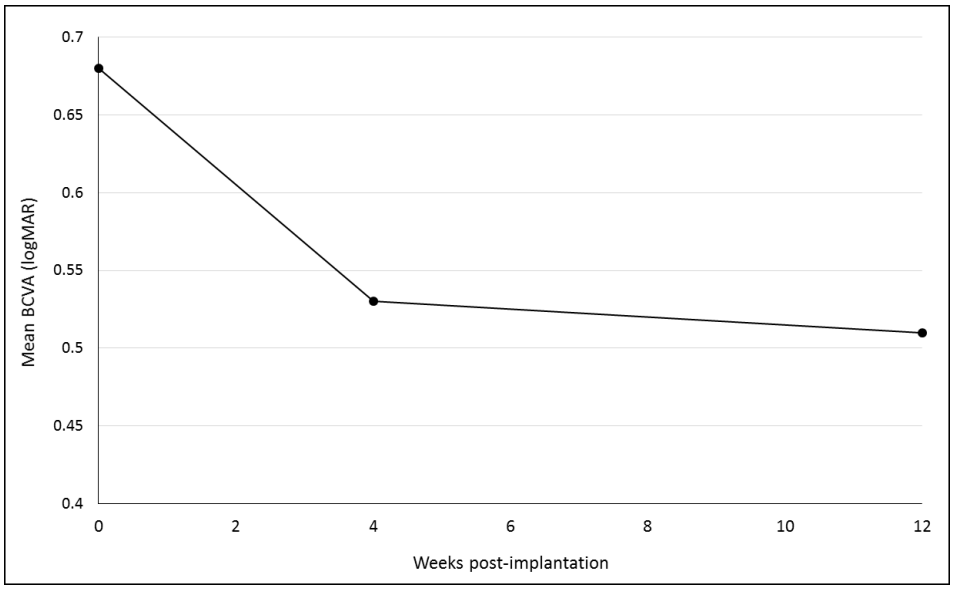
Characteristic (n = 84 eyes/patients)	
Age, years, mean ± SD	52.9 ± 17.5
Female, n (%)	54 (64.3)
Diagnosis, n (%)	
Posterior uveitis	41 (48.8)
Intermediate uveitis	43 (51.2)
Baseline BCVA, logMAR, mean ± SD	0.68 ± 0.47
Final visual acuity, logMAR, mean ± SD	0.62 ± 0.52
Baseline vitreous haze score, mean ± SD	0.89 ± 0.57
Baseline CRT, µm, mean ± SD	462.8 ± 164.8
Baseline IOP, mmHg, mean ± SD	13.9 ± 3.7
Phakic eyes at baseline*, n (%)	36 (58.1)

*The remaining eyes were pseudophakic before treatment.

2.6.7.2 Visual acuity

Mean BCVA was 0.68 ± 0.47 logMAR (Snellen equivalent 20/100) at baseline and improved significantly to 0.53 ± 0.54 logMAR (20/63) by 4 weeks after implantation (P = 0.001) and to 0.51 ± 0.49 logMAR (20/63) by 12 weeks (P < 0.001). However, the beneficial effect on BCVA was lost by the final follow-up visit at week 24 (P = 0.999). There was no significant difference in the improvement in BCVA between eyes with intermediate uveitis and those with posterior uveitis.

Figure 19 Mean BCVA up to 12 weeks post-implantation (Pleyer *et al.*, 2014)



2.6.7.3 Central retinal thickness

Mean CRT improved from 463 ± 165 µm at baseline to 300 ± 110 µm by week 4 (P < 0.001). The improvement from baseline remained significant throughout the follow-up period (P < 0.001 at 12 and 24 weeks' follow-up).

2.6.7.4 Vitreous haze

The proportion of patients with a haze score 0 was significantly increased from baseline at 4 weeks post-implantation (61% vs 19%; P < 0.001); this proportion remained significantly greater than baseline throughout the follow-up (data not presented in source publication).

The mean vitreous haze score was significantly lower than baseline at all follow-up visits from week 4 onwards (P < 0.001 at weeks 4, 12 and 24).

Vitreous haze scores tended to be slightly higher in patients with intermediate uveitis than in those with posterior uveitis but the difference was not significant (P = 0.336).

2.6.7.5 Concomitant systemic corticosteroid and immunosuppressants

Thirty-two patients (38%) were receiving systemic immunomodulatory therapy, with or without corticosteroids, at the time of implantation. Systemic corticosteroid therapy could be discontinued in 8 patients (25%) and could be substantially reduced (to < 10 mg) in a further six patients (19%). Systemic therapies were continued in the other patients. None of the patients required an increased dose of systemic therapy.

2.6.8 Tsang *et al.*, 2016: Retrospective review of patients treated with DEX 700 for macular oedema associated with chronic non-infectious uveitis in Canadian clinical practice

Tsang *et al.* (2016) reported a rapid and sustained improvement following treatment with DEX 700. Seven of 35 eyes (20%) underwent repeat implantation, with a median time to treatment failure of 6 months. Improvements in BCVA and CRT were similar to those observed after first implantation.

2.6.8.1 Study design and baseline characteristics

This was a retrospective chart review of consecutive patients treated with DEX 700 for cystoid macular oedema associated with uveitis affecting the posterior segment of the eye (44). Patients received at least one implant between July 2012 and September 2014 in Ottawa, Canada. Data were collected at baseline (pre-implantation), 1 month after implantation, and then at 3 month intervals up to 12 months after each implantation.

The study included 15 patients who underwent a total of 35 implants in 25 eyes. Ten patients required bilateral implantation, and seven eyes required repeat implantation. The mean follow-up time per eye was 270 days (101–582 days) from first implantation. Fourteen eyes had > 7 months' follow-up. Demographic and baseline characteristics are shown in Table 22.

Table 22 Demographic and baseline characteristics in the study by Tsang *et al.* (2016) (44)

Characteristic (n = 25 eyes in 15 patients)	
Age, years, mean (range)	46.8 (30–64)
Female, n (%)	8 (53.3)
Baseline BCVA, logMAR, mean ± SE (Snellen equivalent)	0.614 ± 0.089 (20/82)
Baseline CRT, µm, mean ± SE	590 ± 28

2.6.8.2 BCVA

Treatment with DEX 700 improved BCVA in 20 of 25 eyes (80%). A significant improvement in mean BCVA was observed at 3 months post-implantation, from 0.614 ± 0.089 logMAR (Snellen equivalent 20/82) at baseline to 0.35 ± 0.10 logMAR (20/45) at month 3. Mean BCVA was numerically superior to baseline at all follow-up visits except month 4. Five of 25 eyes (20%) had a worsening of VA during the follow-up period.

Among the seven eyes that underwent repeat implantation, the improvement from baseline in mean BCVA at 1 month after first implantation was 0.069 ± 0.179 logMAR, whereas the improvement in BCVA following the second implantation was 0.184 ± 0.171 logMAR. The difference in improvement after first and second implantation was not statistically significant.

2.6.8.3 Central retinal thickness

DEX 700 improved CRT in 32 of 35 eyes (91.4%), from 590 ± 28 µm at baseline to 380 ± 28 µm at 1 month post-implantation and 370 ± 3 µm at 3 months ($P < 0.001$); this improvement was maintained throughout follow-up.

Among the seven eyes that underwent repeat implantation, CRT was reduced by 268 ± 76 µm at 1 month after first implantation, and the improvement was 291 ± 74 µm at 1 month after the repeat implantation. The difference in improvement after first and second implantation was not statistically significant.

2.6.8.4 Duration of effect

The median time to treatment failure (defined as the first follow-up with an increase in CRT > 10% and ≥ 50 µm, or the need for a repeat implant) was 6 months; Kaplan–Meier estimates of treatment success were 72% between months 3 and 6, and 54% thereafter.

2.6.9 Adan *et al.*, 2013: Retrospective study of DEX 700 after vitrectomy in the treatment of uveitic macular oedema in Spain

Adan and colleagues (2013) demonstrated that DEX 700 provided improvements across a range of efficacy measures in eyes that have undergone prior PPV.

2.6.9.1 Study design and baseline characteristics

This retrospective chart review was conducted in patients treated with the DEX 700 for macular oedema after systemic medical treatment and/or other intravitreal treatments (36). The study included 17 eyes of 13 consecutive adults treated at the Hospital Clinic of Barcelona, Spain. All patients had previously undergone PPV in the study eye, and patients were excluded if they had active ocular disease, infection, glaucoma, or IOP > 23 mmHg at baseline. CRT and BCVA were evaluated at baseline and at 1, 3, 6, and 12 months post-implantation. Demographic and baseline characteristics are presented in Table 23.

Table 23 Demographic and baseline characteristics in the study by Adan *et al.* (2014) (36)

Characteristic (n = 13 patients, 17 eyes)	
Age, median (range)	60 (19–81)
Female, n (%)	10 (76.9)
Phakic eyes at baseline, n (%)	2 (11.8)
Mean (SD) baseline CRT, µm	461.6 (121.7)

2.6.9.2 BCVA

The median improvement in BCVA at 1 month post-implantation was 1 line (range 0–3; n = 15 eyes; P < 0.01), increasing to 2 lines by 3 months post-implantation; 52.9% of eyes improved by ≥ 2 lines (P < 0.01). This improvement was maintained in 5 eyes (29.4%) at 6 months post-implantation. No eyes lost > 1 line of BCVA from baseline (P = 0.003).

2.6.9.3 Central retinal thickness

The mean CRT at baseline was 461.6 (SD 121.7) µm, which decreased to 277.2 (66.5) µm at 1 month post-implantation (P < 0.01). The reduction in CRT was maintained at 3 months post-implantation (349.9 [143.2] µm, P = 0.01) and remained below baseline at 6 months, although the reduction was no longer statistically significant (394.1 [138.4] µm; P = 0.14). A reduction in CRT > 100 µm was achieved in 10 eyes (62%) at 1 month post-implantation, eight eyes (47.1%) at 3 months, and five eyes (29.4%) at 6 months.

2.6.9.4 Duration of response

Over the follow-up period (mean 9.6 months; range 6–17 months), a relapse of cystoid macular oedema (defined as an increase > 150 µm from the lowest post-implantation CRT) was observed in 8 of 17 eyes (47.1%) after a mean of 6.5 months (3–11 months). These eyes received a repeat implantation. Data relating to outcomes following repeat implantations were not reported.

2.6.10 Pelegrin *et al.*, 2015: Retrospective review of patients treated with DEX 700 for macular oedema secondary to non-infectious uveitis at a single Spanish centre

Pelegrin and colleagues (2015) report outcomes following treatment with DEX 700 for macular oedema secondary to non-infectious uveitis. The study was conducted at a single treatment centre in Spain, and more than half of the patients had intermediate or posterior uveitis (59.5%). DEX 700 provided rapid and sustained efficacy, whether or not patients had undergone prior PPV.

2.6.10.1 Study design and baseline characteristics

Electronic medical records were reviewed from all patients who received DEX 700 at the Hospital Clinic of Barcelona between 2010 and 2013 (37). All patients had macular oedema secondary to non-infectious uveitis (anterior, intermediate, or posterior uveitis or panuveitis). CRT, BCVA, IOP, and vitreous haze were recorded at baseline, 2 weeks, 1, 3, and 6 months and then every 6 months after first implant. Forty-two eyes from 32 consecutive patients were included. The study included 20 eyes that had previously received PPV (an exclusion criteria in the HURON study) and results are

presented separately for eyes with and without prior PPV. Demographic and baseline characteristics are presented in Table 24.

Table 24 Demographic and baseline characteristics in the study by Pelegrin *et al.* (2015) (37)

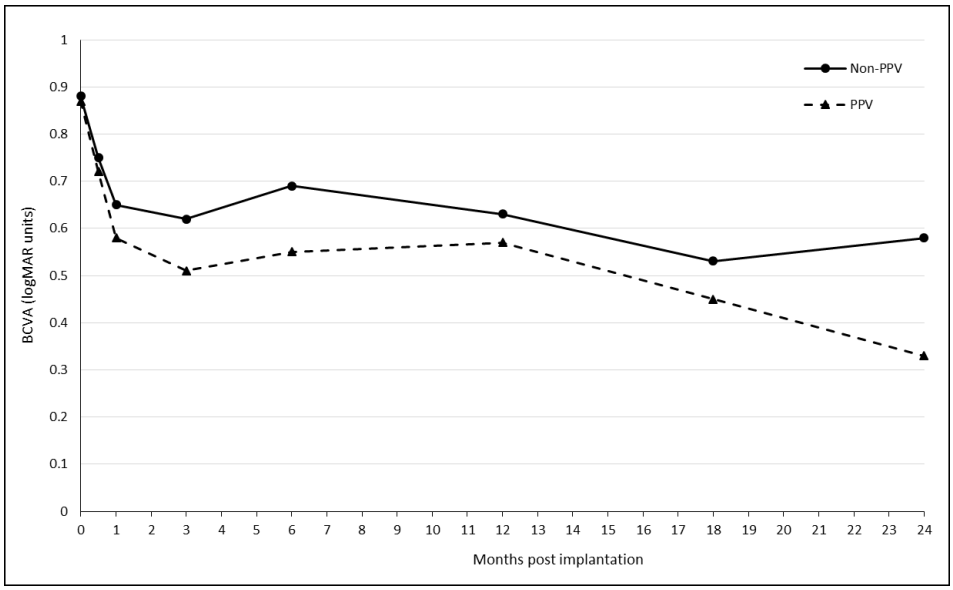
Characteristic (n = 42 eyes in 32 patients)	**Total**	**Prior PPV**	**No prior PPV**	**P value**
Age, years, median (IQR)	54.5 (36–61)	52 (38–61)	55 (36–62)	0.935*
Female, n (%)	31 (73.8)	15 (68.2)	16 (80)	0.491*
Anatomical location, n (%)				
Anterior uveitis	6 (14.3)	Not reported		
Intermediate uveitis	14 (33.3)			
Posterior uveitis	11 (26.2)			
Panuveitis	11 (26.2)			
Indication, n (%)				
Macular oedema	26 (61.9)	15 (68.2)	11 (55)	0.336*
Vitritis	15 (35.7)	6 (27.3)	9 (45)	NR
Macular oedema + vitritis	1 (2.4)	1 (4.5)	0	NR
Previous cataract	4 (9.5)	2 (9.1)	2 (10)	1.000*
Previous glaucoma or ocular hypertension	15 (35.7)	3 (13.6)	12 (60)	0.123*
Previous glaucoma	8 (19)	2 (9.1)	6 (30)	0.003*
Mean estimated BCVA at baseline				
logMAR units (95% CI)	NR	0.87 (0.6–1.1)	0.89 (0.6–1.2)	0.6
Snellen equivalent	NR	20/148	20/155	NR
Estimated mean CRT at baseline, µm (95% CI)	NR	557.3 (246.6–850)	591.8 (234.5–949.1)	0.9
Baseline IOP, mmHg (95% CI)	NR	14.46 (12.6–16.3)	16.2 (14.2–18.3)	0.09

*Fisher's exact test and Mann-Whitney *U*-test.

2.6.10.2 BCVA

BCVA improved in both vitrectomised and non-vitrectomised eyes. Median BCVA was 0.89 (95% CI 0.59–1.18) logMAR (Snellen equivalent 20/155) at baseline in non-vitrectomised eyes and 0.87 (0.60–1.14) logMAR (20/148) in vitrectomised eyes. The maximum improvement was reached at month 3 in both groups, and this improvement was maintained throughout follow-up (Figure 20). The difference between study groups reached statistical significance only at 24 months of follow-up (P = 0.04).

Figure 20 Change in BCVA after DEX 700 (Pelegrin *et al.*, 2015)



2.6.10.3 Central retinal thickness

The maximum decrease in CRT was achieved at month 1 in both non-vitrectomised and vitrectomised eyes (251.2 and 229.9 µm, respectively). This improvement was maintained throughout follow-up: at 24 months post-implantation mean CRT had improved by 189.1 and 273.8 µm in the non-vitrectomised and vitrectomised eyes, respectively. The difference between study groups was significant only at 24 months (P = 0.02).

2.6.10.4 Vitreous haze

The vitreous haze score at baseline was +0.5 to +3.0 in 21 eyes (50%). Two-step improvement or change from +0.5 to 0 was achieved by 66.7% of patients at 1 month, 62% at 3 months, 76.2% at 6 months and 80.1% at 12 months. Changes in the maximum vitreous haze score were similar in non-vitrectomised and vitrectomised eyes during the entire follow-up period (P = 0.706).

2.6.10.5 Repeat implantations

Repeat implantation was required in 19 eyes (45.2%) and there was no difference in the frequency of repeat implantation between non-vitrectomised and vitrectomised eyes. The median time to repeat implantation was 5 months (interquartile range [IQR] 5–6 months). Twelve eyes (28.6%) required two implants, five (11.9%) required three implants, and two(4.8%) had four implants.

2.6.10.6 Concomitant systemic corticosteroid treatment

At baseline, 13 of 32 patients (40.3%) were receiving systemic prednisone and 17 (53.1%) were receiving second-line agents. Prednisone dosing was reduced to < 10 mg per day in all patients at 1 month and this dose reduction was maintained in 78% of patients at 12 months post-implantation. Discontinuation of prednisone treatment was possible in 31.8% of patients at 12 months post-implantation.

2.6.11 Khurana and Porco 2015: Retrospective review of patients treated with DEX 700 for cystoid macular oedema secondary to non-infectious uveitis at a single US centre

Khurana and Porco (2015) reported a rapid and sustained improvement in macular oedema following treatment with DEX 700 in a small cohort of patients at a single US treatment centre. DEX 700 provided benefit in eyes without an epiretinal membrane at baseline but the effect was not significant in eyes with an epiretinal membrane at baseline.

2.6.11.1 Study design and baseline characteristics

This retrospective review by the Northern California Retina Vitreous Associates in the US identified 13 consecutive patients (18 eyes) treated with the DEX 700 for cystoid macular oedema secondary to non-infectious uveitis between July 2011 and November 2012 (38). Patients were followed up for a minimum of 3 months; BCVA, CRT, and IOP were recorded at baseline and 1 and 3 months. The main outcome measure was the cumulative incidence of resolution of cystoid macular oedema at 1 and 3 months after implantation. Secondary outcome measures included changes in VA and CRT, and AEs. Demographic and baseline characteristics are presented in Table 25.

Table 25 Demographic and baseline characteristics in the study by Khurana and Porco (2015) (38)

Characteristic (n = 13 patients, 18 eyes)	
Age, years	
Mean	48
Median	54
Range	27–72
Female, n (%)	10 (77)
Race, n (%)	
White	8 (62)
Latino	2 (15)
Asian	3 (23)
Baseline visual acuity, n (%)	
10/30–10/50	9 (50)
10/60–10/80	7 (39)
10/100–10/150	2 (11)
Baseline CRT, µm	
Median	453
Range	314–778
Baseline vitreous haze score, n (%)	
0	10 (56)
1	6 (33)
2	2 (11)
Baseline IOP, mmHg	
Median	15.6
Range	7–22
Epiretinal membrane present at baseline, n (%)	5 (28)

2.6.11.2 BCVA

Mean BCVA at baseline was 0.449 logMAR (Snellen equivalent 20/60), which improved to 0.238 logMAR (20/30) by 1 month after implantation. DEX 700 provided significant improvement from baseline at 1 month (2.0 lines; IQR 3.3–1.0 lines; P = 0.0016), 3 months (2.1 lines; IQR 3.3–1.2 lines; P = 0.0051), 6 months (2.1 lines; IQR 3.5–0.4 lines; P = 0.014) and 12 months (1.4 lines; IQR 1.9–0.6 lines; P = 0.11). An improvement in BCVA ≥ 2 lines was observed in 47% of eyes at 1 month and 50% of eyes at 3 months.

2.6.11.3 Central retinal thickness

First DEX 700 implantation was associated with complete resolution of cystoid macular oedema in 89% (95% CI 70–95%) of eyes at 1 month and 72% (43–84%) at 3 months.

In eyes without an epiretinal membrane, mean CRT was 502 µm at baseline, improving to 288 µm by 1 month post-implantation. DEX 700 provided significant decreases from baseline at 1 month (190 µm; IQR 275–129 µm; P = 0.00048) and 3 months (228 µm; 295–161 µm; P = 0.0039).

In eyes with an epiretinal membrane, the mean CRT was 399 µm at baseline, decreasing to 298 µm by 1 month post-treatment; however, mean change from baseline was not significant at 1 month (100 µm; IQR 129–38 µm; P = 0.063) or 3 months (33 µm; IQR 66–1 µm; P = 0.50).

The reductions in CRT from baseline after DEX implant were greater in the eyes without an epiretinal membrane than in those with an epiretinal membrane at baseline (P = 0.00078).

2.6.11.4 Vitreous haze

Baseline vitreous haze was grade 1 in 33% of eyes and grade 2 in 11% of eyes. The vitreous haze was grade 0 at 1, 3, 6, and 12 months of follow-up.

2.6.11.5 Repeat implantations

In all patients, the median time to recurrence of cystoid macular oedema was 201 ± 62 (SE) days). Recurrence after a single DEX implant was seen in 65% and 70% of eyes at 6 and 12 months, respectively. In patients with an epiretinal membrane at baseline, the median time to recurrence was 110 days, compared with 338 days for patients without (P = 0.0053).

Repeat implantation was performed in patients with recurrence of cystoid macular oedema and decrease in VA from the previous visit. The number of implants received per patient during the follow-up period ranged from 1 to 4; 56% (10 of 18 eyes) needed two or more implants. Among those who received a second implant, the median time to re-treatment was 300 ± 71 days.

2.7 Ongoing studies

A search of clinical trials.gov identified two RCTs of DEX 700 for the treatment of uveitic macular oedema (NCT02374060 and NCT02623426). Recruitment is ongoing and these studies are scheduled to complete in 2018 at the earliest. The inclusion criteria allow patients with anterior uveitis to be included in these studies.

No ongoing non-randomised studies of interest for this decision problem regarding clinical efficacy/ effectiveness were identified from searches of clinical trials registries.

3 Safety

3.1 Identification of studies reporting safety outcomes

Studies were identified from the searches described in Section 2.2. Briefly, searches were conducted of the PubMed (Medline) database (search terms “dexamethasone intravitreal implant” OR “ozurdex” AND “uveitis”), clinical trials.gov (search terms “dexamethasone” AND “uveitis”), and EudraCT (search terms “dexamethasone AND uveitis”). These searches provided 120 results which were screened for duplicates (3 results excluded) and eligibility according to the criteria described in Section 2.2 (104 results excluded). After screening, 13 publications remained and are reviewed in this section.

3.2 Overview of safety data

The HURON trial demonstrated minimal additional safety issues with the use of DEX 700 compared with sham treatment.

- There were no significant differences in the overall AE rates between DEX 700, DEX 350, and sham (DEX 700, 80.3% [61/76]; DEX 350, 78.4% [58/74]; sham, 68.0% [51/75]; P = 0.170).
- Conjunctival haemorrhage was the most common AE in all treatment groups, and the incidence was significantly greater with DEX 700 and DEX 350 than with sham (DEX 700, 30.3% [23/76]; DEX 350, 17.6% [13/74]; sham, 21.3% [16/75]; P ≤ 0.01). However, the incidence of conjunctival haemorrhage in the study eye that was considered to be related treatment was not significantly different between DEX 700 and sham (25.0% [19/76] vs 13.3% [10/74]).
- The incidence of “IOP increased” and “ocular hypertension in the study eye” was greater with DEX 700 than sham. However, fewer than 10% of patients had IOP values ≥ 25 mmHg, and none at week 26 (except for 3 patients in the sham group); fewer than 5% had IOP values ≥ 35 mmHg.
- The proportion of patients with an increase in IOP ≥ 10 mmHg was significantly greater with DEX 700 than with sham only at week 8. Such increases either did not require treatment or were managed with topical IOP-lowering medications. No patients required incisional surgery for glaucoma.
- Across the whole study period, fewer than 23% of patients treated with DEX required IOP-lowering medication; the majority required only one medication to control IOP.
- Cataracts were reported as an AE in 9 of 62 phakic eyes (15%) in the DEX 700 group and 4 of 55 phakic eyes (7%) in the sham group (not significant; P = 0.769). Three patients had a surgical procedure for cataract in the study eye (one eye in the DEX 700 group and two in the sham group).

Real-world studies have confirmed the low incidence of AEs following treatment with DEX 700.

- Small increases in IOP have been reported in patients receiving DEX 700, although the mean IOP usually remained within normal limits. IOP ≥ 25 mmHg was more common in baseline steroid responders and in eyes without prior PPV.
- Incidence of cataracts following treatment with DEX 700 was low in all identified real-world studies.
- Implant migration to the anterior chamber has been reported in very few patients and only in aphakic or pseudophakic eyes.

- Very few cases of endophthalmitis or retinal detachment were reported after administration of DEX 700.

3.3 Safety in the pivotal HURON trial

The study design, demographic and baseline characteristics, and efficacy outcomes are reported in Section 2.4. All safety data from HURON are taken from the clinical study report (32) or the main trial publication (34).

Of the 77 patients randomised to the DEX 700 group, one was randomised but not treated; of the 76 patients randomised to the DEX 350 group, two were randomised but not treated; of the 76 patients randomised to the sham group, one was randomised but not treated. Thus, the safety analyses are based on a total of 225 patients who received treatment.

Exposure was similar across the three treatment groups. The mean (range) duration was 181.3 (49–225) days for patients in the DEX 700 group, 183.1 (140–216) days in the DEX 350 group, and 181.0 (22–262) days in the sham group.

3.3.1 All adverse events

Overall, there was no significant difference in the rate of AEs across the three treatment groups: 80.3% (61/76) in the DEX 700 group, 78.4% (58/74) in the DEX 350 group, and 68.0% (51/75) in the sham group (P = 0.170).

The most frequently reported AEs (≥ 5% in any treatment group) are summarised in Table 26. Conjunctival haemorrhage was the most common AE in all treatment groups. The incidence was significantly greater with DEX 700 and DEX 350 than with sham (DEX 700, 30.3% [23/76]; DEX 350, 17.6% [13/74]; sham, 21.3% [16/75]; P ≤ 0.01). However, this was a transient event and did not require treatment or affect the use of DEX 700.

The AE profile was generally similar across the three treatment groups. There were no significant pairwise differences in the incidence of any individual AE with the following three exceptions (includes both the study eye and non-study eye): “IOP increased” and “ocular hypertension” were more frequent with DEX 700 and DEX 350 than with sham, and iridocyclitis was more frequent with DEX 700 than DEX 350. In addition, vitreous detachment was reported for three patients in the DEX 350 group but none in the DEX 700 or sham groups (P = 0.035). The majority of AEs were of mild severity. Three patients in the DEX 700 group discontinued from the study because of AEs whereas no patients discontinued from the sham group.

Table 26 Common adverse events reported by ≥ 5% of patients in any treatment group in the HURON study (safety population)

System organ class preferred term[a]	DEX 700 (n = 76)	DEX 350 (n = 74)	Sham (n = 75)
Investigations (study and non-study eyes)			
IOP increased	19 (25.0%)[c]	17 (23.0%)[c]	5 (6.7%)
Eye disorders (study and non-study eye)			
Conjunctival haemorrhage	23 (30.3%)	13 (17.6%)	16 (21.3%)
Eye pain	11 (14.5%)	8 (10.8%)	10 (13.3%)
Iridocyclitis	11 (14.5%)[d]	2 (2.7%)	5 (6.7%)
Uveitis	10 (13.2%)	7 (9.5%)	10 (13.3%)
Ocular discomfort	10 (13.2%)	3 (4.1%)	6 (8.0%)
Cataract	9 (11.8%)	6 (8.1%)	7 (9.3%)
Myodesopsia	7 (9.2%)	5 (6.8%)	5 (6.7%)
Ocular hypertension	6 (7.9%)[b]	7 (9.5%)[c]	0 (0.0%)
Conjunctival hyperaemia	5 (6.6%)	7 (9.5%)	7 (9.3%)
Vision blurred	5 (6.6%)	4 (5.4%)	3 (4.0%)
Eye irritation	4 (5.3%)	2 (2.7%)	3 (4.0%)
Intermediate uveitis	4 (5.3%)	0 (0.0%)	1 (1.3%)
Visual acuity reduced	3 (3.9%)	7 (9.5%)	6 (8.0%)
Macular oedema	3 (3.9%)	4 (5.4%)	6 (8.0%)
Eye pruritus	3 (3.9%)	3 (4.1%)	5 (6.7%)
Cataract subcapsular	2 (2.6%)	5 (6.8%)	4 (5.3%)
Conjunctivitis	1 (1.3%)	3 (4.1%)	4 (5.3%)
Eye swelling	1 (1.3%)	1 (1.4%)	4 (5.3%)
Nervous system disorders			
Headache	5 (6.6%)	6 (8.1%)	5 (6.7%)
Gastrointestinal disorders			
Nausea	0 (0.0%)	2 (2.7%)	4 (5.3%)

[a]System organ class and preferred terms from MedDRA, version 11.1.
[b]Incidence significantly greater with DEX vs sham, P ≤ 0.05.
[c]Incidence significantly greater with DEX vs sham, P ≤ 0.01.
[d]Incidence significantly greater with DEX 700 vs DEX 350, P = 0.01.

As there were no significant differences in AE rates between the DEX 700 and DEX 350 groups, further data presented relate to the commercially available DEX 700 implant.

3.3.2 Treatment-related ocular adverse events in the study eye

The incidence of treatment-related ocular AEs in the study eye was significantly higher in the DEX 700 group than in the sham group (59.2% vs 28.0%; P ≤ 0.035). No treatment-related ocular AEs were reported in the non-study eye. The most frequently reported treatment-related ocular events in the study eye (> 2% in any treatment group) are summarised in Table 27. Conjunctival haemorrhage was the most frequent treatment-related ocular AE, occurring in 25.0% of patients in

the DEX 700 group (19/76) and 13.3% in the sham group (10/75), which was not statistically significant.

Treatment-related ocular events in the study eye were more common overall with DEX 700 than with sham but there were no significant pairwise differences in the incidence of any individual event, with the exception of a higher incidence of treatment-related IOP increase with DEX 700 ($P < 0.001$). In addition, treatment-related eye swelling in the study eye was reported for four patients in the sham group but none in the DEX 700 group (among-group $P = 0.023$).

Treatment-related ocular AEs in the study eye were rated by the investigator as "severe" for the following (n = 1 unless otherwise specified):

- DEX 700: increased IOP (n = 2), ocular hypertension, intermediate uveitis, retinal detachment, endophthalmitis
- Sham: cataract (n = 2), eye pain, retinal detachment, scleral hyperaemia.

Table 27 Treatment-related ocular adverse events in the study eye reported by ≥ 2% of patients in any treatment group in the HURON study (safety population)

System organ class preferred term[a]	DEX 700 (n = 76)	Sham (n = 75)
Investigations (study eye)		
IOP increased	17 (22.4%)[c]	3 (4.0%)
Eye disorders (study eye)		
Conjunctival haemorrhage	19 (25.0%)	10 (13.3%)
Ocular discomfort	9 (11.8%)[d]	3 (4.0%)
Cataract	8 (10.5%)	2 (2.7%)
Ocular hypertension	5 (6.6%)	0 (0.0%)
Eye pain	4 (5.3%)	5 (6.7%)
Conjunctival hyperaemia	3 (3.9%)	6 (8.0%)
Conjunctival oedema	3 (3.9%)	2 (2.7%)
Cataract subcapsular	2 (2.6%)	2 (2.7%)
Myodesopsia	2 (2.6%)	0 (0.0%)
Floaters[b]	2 (2.6%)	0 (0.0%)
Retinal detachment	2 (2.6%)	1 (1.3%)
Eyelid oedema	1 (1.3%)	3 (4.0%)
Eye swelling[e]	0 (0.0%)	4 (5.3%)
Erythema of eyelid	0 (0.0%)	2 (2.7%)

[a]From MedDRA, version 11.1.
[b]Investigator terms for treatment-related events of myodesopsia were floater, floater in visual field and floater in vision.
[c]Incidence significantly greater with DEX 700 vs sham, $P \leq 0.001$.
[d]Incidence significantly greater with DEX 700 vs DEX 350, $P = 0.018$.
[e]Among-group $P = 0.023$.

3.3.3 Serious adverse events

Seven patients in the DEX 700 group and six in the sham group experienced serious AEs (Table 28).

Table 28 Serious adverse events in the HURON study (safety population)

Serious adverse event preferred (verbatim) term	DEX 700 (n = 76)	Sham (n = 75)
Retinal detachment in study eye	2	2
Endophthalmitis in study eye	1	0
Uveitis (worsening uveitis left eye) in study eye	1	0
Cataract in the study eye	0	1
Cerebrovascular accident	1	0
Pelvic inflammatory disease	1	0
Cerebellar infarction	1	0
Pyelonephritis	0	1
Ankylosing spondylitis	0	1
Hypotony of the eye in non-study eye	0	1

3.3.4 Discontinuations due to adverse events

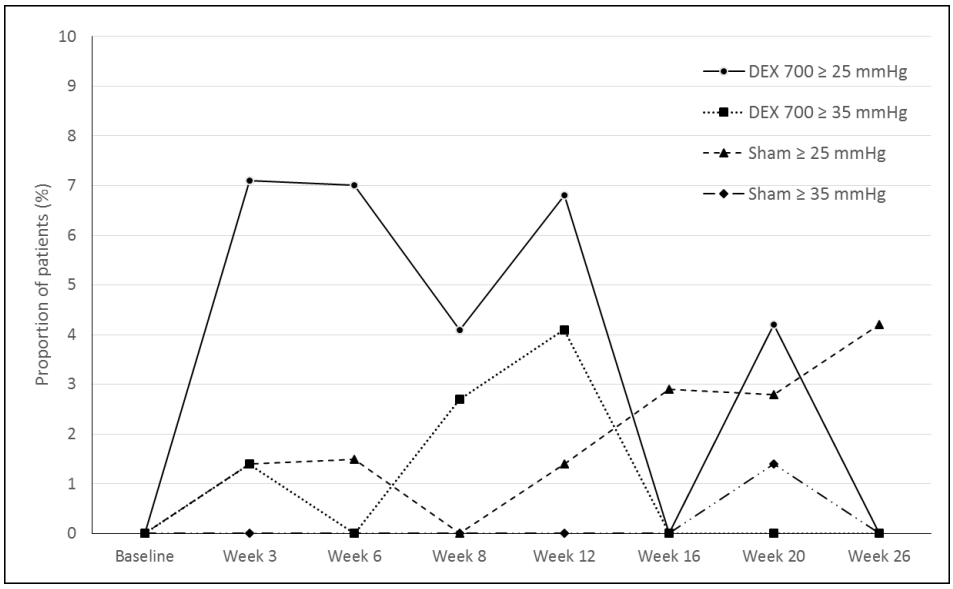
Three patients in the DEX 700 group, but none in the sham group, discontinued the study because of AEs (one case each of retinal detachment, cerebellar infarction, and vitreous opacities).

3.3.5 IOP

The AE term “intraocular pressure increased” in the study eye was reported for 17 patients (22.4%) in the DEX 700 group and three (4.0%) in the sham group. “Ocular hypertension” in the study eye was reported in five patients in the DEX 700 group (6.6%) and no patients in the sham group. No patients receiving DEX 700 reported the AE term “glaucoma” in the study eye, whereas this AE was reported by two patients (2.7%) in the sham group. No patients required incisional surgery, laser trabeculoplasty, or cryotherapy for glaucoma.

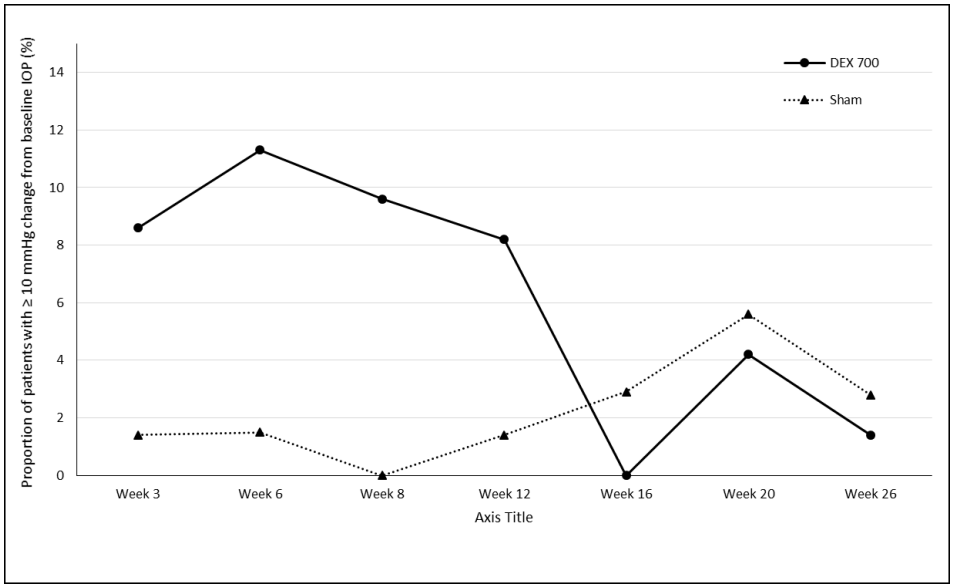
At baseline, there were no statistically significant differences in mean IOP in the study eye between the DEX 700 and sham groups. Figure 21 shows the proportions of patients with IOP ≥ 25 mmHg or ≥ 35 mmHg in the study eye at each treatment visit. At week 3, five patients in the DEX 700 group (7.1%) and 0 patients in the sham group had IOP ≥ 25 mmHg in the study eye; the proportion of patients with IOP ≥ 25 mmHg in the study eye was numerically higher in the DEX 700 group at all visits except weeks 16 and 26. The proportion of patients with IOP ≥ 35 mmHg in the study eye was also higher in the DEX 700 group than the sham group at most study visits, and peaked at week 12 in the DEX 700 group (3 patients; 4.1%) However, the differences were not statistically significant. IOP ≥ 25 mmHg or ≥ 35 mmHg mostly occurred at a single study visit and returned to baseline by the end of the study period.

Figure 21 Proportion of patients with IOP ≥ 25 or ≥ 35 mmHg in the study eye in HURON (safety population)



The proportion of patients with increases in IOP ≥ 10 mmHg from baseline in the study eye (Figure 22) was numerically higher in the DEX 700 group than in the sham group at weeks 3, 6, 8, and 12 but the different was significant only at week 8 (9.6% vs 0.0%; P = 0.013). At weeks 16–26, similar proportions of patients in each group had increases in IOP ≥ 10 mmHg from baseline in the study eye. A significantly greater mean change from baseline IOP was seen with DEX 700 (range 2.4–3.8 mmHg) compared with sham (0.0 to −2.2 mmHg) from day 7 through week 12. At week 26, however, there was no clinically or statistically significant among-group difference in the mean change in IOP from baseline (+0.1 mmHg in the DEX 700 group vs +0.5 mmHg in the sham group).

Figure 22 Proportion of patients with change in IOP ≥ 10 mmHg from baseline in the study eye in the HURON study (safety population)



3.3.6 Cataracts

At baseline, cataracts were reported in 20 of 62 phakic eyes (32%) in the DEX 700 group and 27 of 55 eyes (49%) in the sham group. During follow-up, cataracts were reported as AEs in 9 of 62 phakic eyes (15%) in the DEX 700 group and 4 of 55 phakic eyes (7%) in the sham group (not significant; P = 0.769). Three patients had a surgical procedure for cataract in the study eye (one eye in the DEX 700 group and two in the sham group).

3.4 Real-world safety evidence

3.4.1 Tomkins-Netzer *et al.*, 2014: Retrospective review of patients undergoing treatment and re-treatment with DEX 700 for non-infectious uveitis in UK clinical practice at two treatment centres

The study design, demographic and baseline characteristics, and efficacy results are reported in Section 2.6.1.

3.4.1.1 IOP

Mean IOP remained within normal limits throughout follow-up: 16.5 ± 0.7 mmHg at baseline; 19 ± 1.4 mmHg at 2 months; 14.3 ± 1.2 mmHg at month 12 (35).

At baseline, seven eyes were known to develop ocular hypertension in response to corticosteroids ("steroid responders", Table 13). However, 2 months after the first implant only three eyes demonstrated increased IOP of > 21 mmHg (two steroid responders and one not previously diagnosed), one with IOP > 25 mmHg that responded to topical IOP-lowering medication. The other five known steroid responders showed no increase in IOP after the first implantation. After second implantation, four eyes demonstrated IOP > 25 mmHg within 2 months (three known steroid responders). There were no cases of increased IOP after the third implant. The frequency of increased IOP was 0.13 per eye-year.

3.4.1.2 Cataracts

One of 21 phakic eyes developed new posterior subcapsular opacities following the first implant but there were no new cases of cataract development after the second implant. One further eye developed posterior subcapsular opacities following a third implant.

3.4.1.3 Other adverse events

One case of implant migration was reported in an eye that had undergone previous cataract extraction. The implant was recovered from the bottom of the anterior chamber and caused localised corneal decompression but with no increase in IOP.

3.4.2 Zarranz-Ventura *et al.*, 2014: Multicentre retrospective review of patients treated with DEX 700 for non-infectious uveitis in UK and Spanish clinical practice

The study design, demographic and baseline characteristics, and efficacy results are reported in Section 2.6.2.

3.4.2.1 IOP

Raised IOP (≥ 21 mmHg) was the most frequently reported AE (33/82 eyes, 40.2%); IOP-lowering medication was required in 32 (39%) (15).

At baseline, the mean IOP was 14.1 (SD 4) mmHg, increasing to 18.0 (8) mmHg at week 2 (P < 0.001), 18.0 (7) mmHg at month 1 (P < 0.001), 15.9 (5) mmHg at month 3 (P = 0.01), 14.4 (4) mmHg at month 6 (P = 0.62), and 14.6 (4) mmHg at month 12 (P = 0.43). The probability of IOP ≥ 21 mmHg was 32% at month 1 and 41% at month 3. The probability of IOP ≥ 25 mmHg also increased from month 1 to month 3 (19% and 23%, respectively), while the probability of IOP ≥ 35 mmHg was 7% at months 1 and 3. The probability of increase in IOP of ≥ 5, ≥ 10, or ≥ 15 mmHg was 46%, 23%, and 12%, respectively. The probabilities increased at month 3 to 53%, 30%, and 13%, respectively.

3.4.2.2 Cataracts

The proportion of pseudophakic eyes increased from 51.2% (42/82 eyes) at baseline to 56.1% (46/82 eyes) at final follow-up, suggesting that 4 of 82 eyes (4.9%) had undergone cataract surgery after implantation. It should be noted that these patients did not necessarily develop the cataract during the study period and may have had pre-existing cataracts.

3.4.2.3 Other adverse events

Two cases (2/142 eyes; 1.4%) of implant migration to the anterior chamber were reported, one in an aphakic eye and one in a pseudophakic eye with iris-claw intraocular lens. Three eyes (2.1%) developed vitreous haemorrhage, three cases of hypotony were reported (2.1%; two in vitrectomised eyes) and one case of endophthalmitis (0.7%).

3.4.3 Miserocchi *et al.*, 2012: Retrospective study of patients treated with DEX 700 for chronic posterior non-infectious uveitis at a single Italian centre

The study design, demographic and baseline characteristics, and efficacy results are reported in Section 2.6.3.

3.4.3.1 IOP

Elevated IOP was observed in three of 14 eyes in 12 patients (all < 30 mmHg), all of which occurred within 2 weeks of implant, were transient, and were controlled with topical IOP-lowering medication (40).

3.4.3.2 Cataracts

No development or worsening of cataracts, or patients requiring cataract surgery, were reported in this study.

3.4.3.3 Other adverse events

One case of subconjunctival haemorrhage was reported, which resolved spontaneously within 1 month. Vitreous haemorrhage occurred in one patient receiving anticoagulant therapy for chronic atrial fibrillation and resolved after 1 month.

3.4.4 Palla *et al.,* 2015: Retrospective review of patients treated with DEX 700 for non-infectious uveitis at a single Indian centre

The study design, demographic and baseline characteristics, and efficacy results are reported in Section 2.6.4.

3.4.4.1 IOP

Three eyes (15%) developed IOP > 21 mmHg and two (10%) developed IOP ≥ 25 mmHg at week 6, one of which was a steroid responder. All cases were manageable with medication (41).

3.4.4.2 Cataracts

Five eyes (25%) required cataract surgery within the 1 year follow-up period, and two eyes (10%) within 6 months.

3.4.4.3 Other adverse events

One case of pars planitis (5%) was diagnosed, which required vitrectomy at 8 months post-implantation.

3.4.5 Lam *et al.*, 2015 (NCT01805323): Multicentre retrospective chart review of patients treated with DEX 700 for macular oedema in Canadian clinical practice

The study design, demographic and baseline characteristics, and efficacy results are reported in Section 2.6.5. AEs were reported in 5 of 20 patients (25%) with uveitis.

3.4.5.1 IOP

increased IOP was the most commonly reported AE (2 of 20 patients, 10%) (42). Among eyes in the uveitis cohort with a history of steroid response, 37.5% experienced an increase in IOP ≥ 10 mmHg following implantation. The same proportion of eyes presented with absolute IOP ≥ 25 mmHg, while 12.5% of eyes with a history of steroid response presented with IOP ≥ 35 mmHg. Topical IOP-lowering medications were required for 62.5% of eyes with a history of steroid response in the uveitis cohort.

3.4.5.2 Cataracts

One of 20 patients developed a subcapsular cataract following treatment with DEX 700. Cataract surgery was performed in 5 of 11 phakic eyes (45.5%) in the uveitis cohort following implantation.

3.4.5.3 Other adverse events

One of 20 patients developed a retinal detachment which was repaired surgically, and treatment with DEX 700 was continued. A uveitis flare was reported as a serious AE in one patient in the uveitis cohort.

3.4.6 Nobre-Cardoso *et al.*, 2016: Retrospective review of patients treated with DEX 700 for non-infectious uveitic macular oedema at a single French centre

The study design, demographic and baseline characteristics, and efficacy results are reported in Section 2.6.6.

3.4.6.1 IOP

IOP > 21 mmHg occurred in 36.3% of eyes, IOP > 25 mmHg in 31%, and IOP > 30 mmHg in 6.9% (43); all cases responded to topical IOP-lowering medications. Eyes with a history of steroid response accounted for 10 of the 15 eyes that developed ocular hypertension following implantation.

3.4.6.2 Cataracts

Three eyes (in three patients) required cataract surgery during the follow-up period, all in eyes that had received repeat implantations. Subcapsular cataracts developed at 6, 7, and 12 months after first implantation.

3.4.6.3 Other adverse events

One patient who was taking concomitant antiplatelet medication (clopidogrel) developed vitreous haemorrhage that required prompt PPV. No cases of implant migration, endophthalmitis, or retinal detachment were reported.

3.4.7 Pleyer *et al.*, 2014: Prospective non-comparative case series including patients treated with a single DEX 700 for non-infectious intermediate or posterior uveitis at two centres in Germany

The study design, demographic and baseline characteristics, and efficacy results are reported in Section 2.6.7.

3.4.7.1 IOP

Mean IOP was 13.9 ± 3.7 mmHg at baseline, and no patients had IOP > 21 mmHg (39). During the follow-up period, 3 patients (4%) developed IOP ≥ 35 mmHg and 13 (16%) had IOP ≥ 25 mmHg.

The proportion of patients requiring IOP-lowering medication increased from 21% at baseline to a maximum of 42% at 12 weeks post-implantation, decreasing to 28% at 24 weeks, in line with the falling steroid concentration released from DEX 700.

Intermediate uveitis was significantly associated with a stronger secondary IOP increase compared with posterior uveitis (P = 0.003). Baseline IOP did not differ between eyes with intermediate or posterior uveitis.

3.4.7.2 Cataracts

At baseline, 25 eyes (42%) were pseudophakic, and subcapsular cataract was present in 3 (6%) of the phakic eyes. These pre-existing lens changes progressed in 2 eyes (4%) during follow-up, and mild subcapsular cataract developed in 7 phakic eyes (14%). Surgery was not required in any case.

3.4.7.3 Other adverse events

The study authors stated that “few patients” (number not reported) experienced immediate conjunctival haemorrhage, which cleared rapidly. One patient was kept on anticoagulant medication and experienced acute mild intravitreal bleeding which subsided within 4 weeks and did not affect visual function. No patients developed endophthalmitis or uveitis flare-up related to the implant.

3.4.8 Tsang *et al.*, 2016: Retrospective review of patients treated with DEX 700 for macular oedema associated with chronic non-infectious uveitis in Canadian clinical practice

The study design, demographic and baseline characteristics, and efficacy results are reported in Section 2.6.8.

3.4.8.1 IOP

Patients with baseline IOP > 21 mmHg were excluded from the study (44). No patients had an increase in IOP of > 10 mmHg or developed absolute IOP > 21 mmHg.

3.4.8.2 Cataracts

Posterior subcapsular opacities that were present prior to implantation in two of 15 patients progressed. No cases of new cataract occurred during follow-up.

3.4.8.3 Other adverse events

An implant was injected into the body of the lens in one eye, which was successfully treated with vitrectomy and lensectomy. The implant became fragmented in the eye. During the study period, one eye developed a macular hole and three eyes (three patients) developed an epiretinal membrane. There were no cases of endophthalmitis or retinal detachment.

3.4.9 Adan *et al.*, 2013: Retrospective study of DEX 700 after vitrectomy in the treatment of uveitic macular oedema in Spain

The study design, demographic and baseline characteristics, and efficacy results are reported in Section 2.6.9.

3.4.9.1 IOP

Increased IOP occurred as an AE in 47.1% of study eyes (36). IOP between 22 and 30 mmHg occurred in 41.1% of eyes, and a single eye (5.9%) developed IOP between 30 and 40 mmHg. No eyes developed IOP > 40 mmHg. All cases were treated with topical antihypertensive medication and IOP normalised within 8 weeks post-implantation. One patient required a surgical procedure to control IOP.

3.4.9.2 Cataracts

One patient (5.9%) required cataract surgery during the follow-up, for a cataract that was present before implantation.

3.4.9.3 Other adverse events

Transient hypotony that resolved without treatment was reported in two eyes (11.8%). Anterior chamber displacement of the implant was reported in one aphakic eye (5.9%). Retinal detachment was reported 5 months post-implantation in one eye (5.9%). No eyes developed vitreous haemorrhage or endophthalmitis during the study period.

3.4.10 Pelegrin *et al.*, 2015: Retrospective review of patients treated with DEX 700 for macular oedema secondary to non-infectious uveitis at a single Spanish centre

The study design, demographic and baseline characteristics, and efficacy results are reported in Section 2.6.10.

3.4.10.1 IOP

IOP > 21 mmHg was observed in 20 eyes (47.6%) – 8 non-vitrectomised eyes (36.4%) and 12 vitrectomised eyes (60%); the difference between groups was not significant (P = 0.216) (37).

Mean baseline IOP was 16.21 mmHg in non-vitrectomised eyes and 14.46 mmHg in vitrectomised eyes. IOP was significantly higher in non-vitrectomised then vitrectomised eyes at 3 months (difference of 3.5 mmHg [95% CI 0.4–6.5]; P = 0.025), 6 months (3.37 mmHg [1.26–5.48]; P = 0.002), and 12 months (3.5 mmHg [0.8–6.3]; P = 0.013).

Glaucoma was present at baseline in two non-vitrectomised eyes (9.1%) and six vitrectomised eyes (30%). Ocular hypertension was present in one (4.5%) and six eyes (30%), respectively, requiring an increase in hypotensive medication after implantation. New hypotensive treatment was required for six non-vitrectomised and three vitrectomised eyes.

3.4.10.2 Cataracts

Four eyes had cataracts before implantation which progressed post-implant, three requiring surgery.

3.4.10.3 Other adverse events

Implant migration to the anterior chamber occurred in two eyes (4.7%; one aphakic eye and one with an iris-claw intraocular lens). Three eyes (7.1%) developed transient hypotony, which resolved without treatment, and vitreous haemorrhage occurred in three eyes (7.1%).

3.4.11 Khurana and Porco 2015: Retrospective review of patients treated with DEX 700 for cystoid macular oedema secondary to non-infectious uveitis at a single US centre

The study design, demographic and baseline characteristics, and efficacy results are reported in Section 2.6.11.

3.4.11.1 IOP

There were no significant changes in mean IOP at 1, 3, 6, and 12 months post-implantation (38).

IOP ≥ 25 mmHg occurred in two eyes (11%) during the first 90 days after first implant but there were no cases of IOP ≥ 35 mmHg. One eye had an increase in IOP > 10 mmHg from baseline. All cases of increased IOP were managed with topical hypotensive medications. Four patients required new hypotensive treatments during follow-up but none required surgery.

3.4.11.2 Cataracts

One of 10 phakic eyes at baseline had an increase in lens opacity at approximately 9 months post-implantation, representing progression of an existing cataract.

3.4.11.3 Other adverse events.

There were no episodes of retinal detachment, hypotony, or migration of the implant to the anterior chamber. No serious AEs occurred in any patients.

3.4.12 Ongoing studies

A long-term safety study examining the use of DEX 700 in real-world clinical practice was identified in the search of clinicaltrials.gov (NCT01539577; Allergan sponsor ID: 206207-025). The primary completion date was March 2016; the clinical study report is expected to be available in September 2016.

4 Clinical interpretation of the evidence

4.1 Challenges in conducting indirect comparisons of effectiveness

This section addresses the issues that need to be taken into consideration when conducting indirect comparisons of effectiveness across trials in posterior segment uveitis using network meta-analysis methods.

4.1.1 Improvements in visual acuity depend on baseline severity

Greater gains in VA can be achieved in patients with worse VA at baseline, making it difficult to compare improvements in VA across studies with different baseline VA severity. Zarranz-Ventura and colleagues (2014) noted that their study had a lower proportion of eyes with good baseline vision (> 70 letters, < 0.3 logMAR) – 11%, vs 21% in HURON (15); patients with a baseline VA ≥ 70 letters would be unable to achieve a 15 letter improvement because of a ceiling effect.

The severity of cystoid macular oedema at baseline also affects the magnitude of VA improvement. The real-world study reported by Zarranz-Ventura and colleagues (2014) included a greater proportion of patients with uveitic central macular oedema than did the HURON trial. The authors hypothesised that any improvement in central macular oedema is likely to lead to a greater VA improvement than would be observed in a patient without central macular oedema. Therefore, the

proportion of patients with central macular oedema is likely to be an important determinant of the magnitude of VA improvement and needs to be controlled for when making comparisons across studies.

4.1.2 Use of different baseline and rescue medications across trials

The use of systemic therapies at baseline may contribute to differences in efficacy rates seen in different studies. It is therefore important to control for differences in baseline exposure to systemic corticosteroids and immunosuppressants when attempting indirect comparisons across studies. The use of systemic treatment at baseline in the real-world study reported by Zarranz-Ventura and colleagues (2014) was more than double that in the HURON trial (53.9% vs 25.9%). However, data from the HURON trial indicate that the efficacy of DEX 700 was similar irrespective of whether patients had prior exposure to systemic corticosteroids or immunosuppressants. Given the paucity of RCT data relating to systemic corticosteroids or immunosuppressants, it is unlikely that the impact of prior exposure would be known for other therapies, so caution is required when making comparisons across studies, because of differences in baseline exposure.

It is also challenging to compare the efficacy of DEX 700 with that of other therapies using network meta-analysis because of the study design of HURON. HURON was a sham-controlled study, necessitating the availability of systemic rescue medication throughout its duration (high-dose systemic corticosteroids and immunosuppressants); it is therefore difficult to compare the efficacy of DEX 700 with other therapies with different trial designs via network meta-analysis.

4.1.3 Use of different efficacy endpoints

The primary endpoint in the HURON trial was the proportion of patients with vitreous haze score 0 whereas other studies have used other endpoints to assess efficacy. For example, the endpoint in the trials of adalimumab was time to treatment failure. Given the paucity of RCT evidence for systemic immunosuppressants, and the range of endpoints used where trials are available, it will be challenging to compare efficacy across trials via network meta-analysis. In this respect, changes in VA should be assessed consistently in trials. However, as noted in Section 4.1.1, improvement in VA depends on the severity at baseline so it not an ideal outcome measure for comparing efficacy via network meta-analysis.

4.1.4 Comparing HRQL improvements across studies with unilateral and bilateral involvement

The comparison of HRQL across studies is hampered by differences in the proportion of patients with bilateral uveitis, as the magnitude of HRQL improvement depends on whether patients have unilateral or bilateral uveitis. None of the observational studies identified for DEX 700 appear to have included validated HRQL measures, so data on the impact of the worse- and best-seeing eye are limited (45).

4.2 Importance of visual acuity as an endpoint

The NICE scope highlights VA as the most important endpoint because it most closely correlates with the HRQL of patients. Vitreous haze was used as the primary endpoint in the HURON trial; this is a validated endpoint that was selected for the regulatory approval of DEX 700. VA was a secondary

endpoint in the HURON trial. As outlined by Lightman and colleagues (2013), the HURON trial showed that treatment-related improvements in inflammation and VA in patients receiving DEX 700 resulted in improvements in visual functioning and wellbeing (33).

4.3 Comparison of RCT efficacy and real-world effectiveness of DEX 700

As outlined in Section 2.6, the effectiveness of DEX 700 in real-world clinical practice has been studied extensively over the 5 years since it received marketing authorisation. Observational data from real-world clinical practice largely reinforce the clinical profile of DEX 700 seen in the HURON pivotal trial. Nevertheless, it is important to note some of the differences between results from the HURON trial and those obtained in clinical practice, and the implications of these differences.

A key difference is that patients with vitreous haze scores < 1.5 are typically treated with DEX 700 in clinical practice, whereas these patients were excluded from the HURON trial. Zarranz-Ventura and colleagues (2014) and Nobre-Cardoso and colleagues (2016) note that the main use of DEX 700 in clinical practice is in patients with uveitic cystoid macular oedema in eyes with quiescent or minimal vitritis. Pleyer and colleagues (2014) describe a population in which almost half of the eyes had posterior uveitis, compared with fewer than 20% of the eyes in HURON. The study authors suggest that the lower proportion of patients with intermediate uveitis in the real-world study could account for the lower mean vitreous haze score at baseline and a faster improvement in the score. The studies by Pleyer and colleagues (2014) and Nobre-Cardoso and colleagues (2016) also highlight the substantially higher CRT among the population of patients with cystoid macular oedema in clinical practice compared with the population of HURON.

Zarranz-Ventura and colleagues (2014) considered the use of DEX 700 in patients with uncontrolled systemic involvement (e.g. multiple sclerosis) and included patients with anterior uveitis complicated by cystoid macular oedema, groups that were excluded from the HURON trial. Nobre-Cardoso and colleagues (2016) highlight that their study population was predominantly eyes with panuveitis, another category excluded from HURON, and that the majority had active disease requiring systemic immunosuppression at baseline (66.7%, compared with only 26% in HURON). The severity of the condition of the population in the study by Nobre-Cardoso and colleagues (2016) is likely to account for the substantially shorter duration of effect observed, with almost 70% of eyes relapsing within 6 months.

It is difficult to compare the magnitude of improvements in VA obtained in HURON with those achieved in real-world clinical practice because of differences in the proportions of patients with cystoid macular oedema or taking systemic therapy at baseline, and baseline VA severity. However, it is reassuring that VA improvements have been observed in all studies, regardless of these factors.

Data from clinical practice also demonstrate the efficacy and safety of bilateral treatment, whereas in HURON only the right eye was treated in patients with bilateral disease where both eyes were eligible for treatment with DEX 700. Data from clinical practice also demonstrate the efficacy and safety of repeat administrations, which were not obtainable from the single injections observed in the HURON trial.

It is important to note that the safety profile of DEX 700 is well characterised from long-term use in other indications. This is important given the relatively small patient populations in trials in posterior segment uveitis.

The lack of available alternatives in clinical practice may mean that a wider range of patients are treated in clinical practice than were included in the HURON trial. Pleyer and colleagues (2014) suggest that the higher rate of increased IOP in their study compared with that observed in HURON (37% vs 22% in the study eye) may reflect the inclusion of patients with prior need for antiglaucoma medications (who were excluded from HURON). Similarly, higher proportions of patients experienced raised IOP in real-world studies, including 36% in the study by Nobre-Cardoso and colleagues (2016) and 37% in the study by Zarranz-Ventura and colleagues (2014).

The 2014 study by Pleyer and colleagues showed that patients with intermediate uveitis were at greater risk of developing raised IOP than were those with posterior uveitis (P = 0.013 at 12 weeks post-implantation). The population in this real-world study included fewer eyes affected by intermediate uveitis, which may contribute to the lower risk of raised IOP seen in this study compared with the HURON population, suggesting that another factor in the real world population may be contributing to the increased incidence of raised IOP outside of the clinical trial setting. It should be emphasized that all cases of raised IOP were easily managed with topical medications.

4.4 Benefits of local versus systemic therapy

The difficulty of achieving target drug concentrations in the posterior segment of the eye means that local therapy is preferred to systemic therapy (in the absence of systemic disease requiring treatment). DEX 700 intravitreal implants provide the appropriate target concentrations in the posterior segment of the eye while minimising systemic side effects. The risk–benefit profile of systemic corticosteroids is not favourable for long-term use. Data from the UK General Practice Research Database (GPRD) show that the risk of fractures is related to the daily dose of corticosteroids, and that patients receiving > 7.5 mg prednisolone per day have the highest risk of fractures (46). The fracture risk is rapidly reversed with cessation of corticosteroid use, indicating that corticosteroid-sparing treatments for uveitis, such as DEX 700, will be beneficial. Data from GRPD also show that there is a significant association between use of systemic corticosteroids and cardiovascular and cerebrovascular events (47). The association was strongest for current use rather than for recent and past use, and the risk is highest in patients receiving the highest dose of corticosteroids. Cumulative dose was less important than current daily dose, which suggests that cardiovascular benefits may be seen with corticosteroid-sparing treatments even where there has been high cumulative exposure to systemic corticosteroids. Furthermore, the study showed that the risk of cardiovascular and cerebrovascular events was increased in patients with rheumatoid arthritis, chronic obstructive pulmonary disease or “other” diseases, which suggests that the impact of corticosteroids on cardiovascular risk may also be applicable to patients with uveitis.

Use of high-dose systemic corticosteroids has also been shown to increase the incidence of diabetes (48). In the MUST trial comparing the fluocinolone implant with systemic therapy, the 54 month incidence of diabetes was 2.0% in the implant arm versus 5.7% in the systemic therapy arm (49). This difference was not statistically significant (HR 0.4; 95% CI 0.1–1.8) so larger, better-powered studies are needed to assess any difference in the incidence of diabetes between local and systemic corticosteroid therapy.

Mental health can also be adversely affected by use of systemic corticosteroids (50). Psychiatric symptoms, including mania, depression, and mood disturbances, appear to be dose dependent. A study in the US that assessed AEs associated with long-term corticosteroid use found that approximately 30% of patients with a cumulative prednisone-equivalent dose of 1.7 g self-reported

mood problems, which rose to approximately 60% for patients receiving a cumulative prednisone-equivalent dose of 4.7 g.

The main disadvantage of systemic immunosuppressant therapy is the risk of malignancy, given the need for long-term therapy. Yates and colleagues (2015) conducted a retrospective cohort study of 132 patients treated for ≥ 6 months with systemic immunosuppressant therapy and 58 patients treated with systemic corticosteroids only for uveitis (51). Twenty-five malignancies were observed in 17 patients during a median follow-up of 7.34 years, equivalent to 2.10 per 100 person-years in the immunosuppressant group and 0.43 per 100 person-years in the corticosteroid-only group. The most common malignancies were non-melanoma skin cancers and non-Hodgkin's lymphoma. Compared with the corticosteroid treatment-only group, the immunosuppressant group was at an increased risk of any malignancy (adjusted HR 4.36; 95% CI 1.02–18.7). No cancer-related deaths occurred in the study. This study indicates that, among 100 patients treated with systemic immunosuppressants, an additional 1.67 malignancies would be observed per year. The sample size of this study means that it not possible to assess the relationship between cumulative dose of systemic immunosuppressants and malignancy risk so it is difficult to quantify the expected benefit of systemic immunosuppressant-sparing therapies in reducing malignancy risk.

4.5 Benefit of DEX 700 in posterior segment uveitis and other indications

A favourable cost–utility profile has been demonstrated for DEX 700 in RVO, to the extent that it has been recommended by NICE in that indication (52). NICE recommended DEX 700 as an option for the treatment of:

- macular oedema following CRVO
- macular oedema following BRVO when treatment with laser photocoagulation has not been beneficial, or is not considered suitable because of the extent of macular haemorrhage.

The clinical evidence for this technology appraisal (TA229) was a pooled analysis of the GENEVA 008 and GENEVA 009 studies (52). These data demonstrated that, in patients with CRVO, 21.3% in the DEX 700 group achieved improvement in BCVA from baseline ≥ 15 letter by day 30, compared with 6.8% in the sham group ($P < 0.001$), increasing to 28.7% by day 60 in the DEX 700 group (vs 8.8% in the sham group; $P < 0.001$). However, the difference between DEX 700 and sham groups was not statistically significant at days 90 or 180.

Whilst it is difficult to make indirect comparisons between data from the GENEVA and HURON trials, because of differences in the recruitment criteria, outcome measures and population characteristics, we note that the BCVA results from the HURON study in patients with posterior segment uveitis are similarly positive: a significantly higher proportion of patients achieved ≥ 15 letter improvement from baseline compared with sham at week 3 (32.5% vs 3.9%; $P < 0.001$). The proportion of patients achieving ≥ 15 letter improvement in BCVA from baseline in the DEX 700 group peaked at week 8 (42.9%, vs 6.6% in the sham group; $P < 0.001$), and the difference between the groups remained significant through to week 26 (37% vs 13.2%; $P < 0.001$) (32).

These data suggest that the absolute and incremental gains in BCVA are greater in posterior segment uveitis than in CRVO.

5 Cost effectiveness

This submission does not include a cost–utility model for DEX 700 in uveitis. DEX 700 has been recommended by NICE for the treatment of RVO. The costs per patient associated with DEX 700 treatment for RVO and posterior segment uveitis are comparable, while the absolute and incremental gains in VA, which in turn closely correlated with vision-related HRQL, are also greater in posterior segment uveitis than for RVO (see Section 4.5). On this basis, it is reasonable to assume that DEX 700 would represent a cost-effective use of NHS resources for the treatment of posterior segment uveitis, according to NICE's usual criteria.

5.1 Costs of treatment with DEX 700

The UK list price for DEX 700 is £870 for the implant and applicator (excluding value added tax). Intravitreal implant are assumed to be administered in the outpatient setting, at a cost of £109 (NHS National Tariff 2016–17 BZ23Z: Minor Vitreous Retinal Procedures, outpatient procedure) (53). This is consistent with the recent NICE appraisal of DEX 700 for DMO (54). Therefore, the drug acquisition and administration cost for one course of DEX 700 for unilateral treatment is £979. It is assumed that bilateral therapy would require two separate procedures and would therefore cost twice as much (£1,958 per treatment course).

5.1.1 Mean number of re-treatments and time to re-treatment with DEX 700

It is necessary to estimate the mean number of re-treatments and time to re-treatment with DEX 700 in order to estimate the mean annual cost of treatment. Zarranz-Ventura and colleagues (2014) have reported data regarding the mean number of re-treatments and time to re-treatment in real-world clinical practice for patients completing 12 months of follow-up:48.1% received only one injection per eye, and the mean number of injections per eye was 1.64. The mean number of injections was therefore assumed to be 1.64 per year for patients requiring unilateral treatment, and 3.28 injections per year for those requiring bilateral treatment.

5.1.2 Cost of monitoring DEX 700

Monitoring consists of outpatient visits for visual function monitoring to assess the efficacy of the implant and the need for re-treatment, and to monitor the risk of AEs. There are no blood monitoring requirements with DEX 700 because it is a local therapy; monitoring for AEs is conducted alongside regular visual function monitoring follow-ups. After the injection visit, patients are followed up at weeks 4, 12, 20, 20–28 (to consider re-injection), 32, 40, and 48. Patients receiving two injections per year would therefore require eight visits annually (six monitoring visits plus two injection visits). The mean number of injections per year is estimated to be 1.64 (see Section 5.1.1). Therefore, given that 1.64 is fewer than the two injections assumed in this monitoring schedule, the mean number of monitoring visits was assumed to be $[1.64 \div 2] \times 6 = 4.92$ per year.

For a patient receiving bilateral treatment, it is assumed that monitoring visits would include assessment of both eyes so these patients would also have an average of 4.92 monitoring visits per year and 3.28 injection visits.

Assuming a cost of £64 per outpatient ophthalmology follow-up visit for monitoring (WF01A) and a cost of £109 per injection visit, the annual cost for administration and monitoring of DEX 700 would be £494 for unilateral treatment and £672 for bilateral treatment.

5.1.3 Cost of treating adverse events of DEX 700

As outlined in Section 3.4, raised IOP is one of the most commonly reported AEs in real-world clinical practice with DEX 700. However, the costs of management are likely to be low, as in most patients IOP is controlled with medication, without the need for more expensive treatment interventions such as surgery. The cost of managing IOP elevation using bimatoprost would be £11.71 per month per eye (100 µg/mL; 3 mL pack) (55). Given that not all patients with elevated IOP require continuous treatment, the mean annual cost of managing IOP elevation while on DEX 700 is likely to be low.

Other serious AEs such as endophalmitis and retinal detachment have been observed in clinical practice in patients receiving DEX 700. However, the low frequency of these events means that cost of managing these AEs across a cohort of treated patients is likely to be low.

5.1.4 Cost impact of reductions in systemic therapy with DEX 700

The available data do not facilitate accurate estimation of the cost offsets that may be achieved by reducing concomitant systemic therapy. If DEX 700 is positioned as a second-line alternative to immunosuppressant therapy, the most likely dose reductions in systemic treatment would be in corticosteroids; however, the drug acquisition costs of prednisolone are low. More significant cost offsets are more likely be achieved through the reduction in the risk of AEs such as osteoporosis, diabetes and cardiovascular events with reductions in the doses of corticosteroids over time for patients whose uveitis is controlled with DEX 700. Data are not available to quantify the mean reduction in prednisolone dose that would be achieved in the long-term for these patients, or the cost implications of that dose reduction. Therefore, this potential benefit of DEX 700 is difficult to include in the modelling of cost-effectiveness.

5.2 Costs of treatment with comparators

The annual drug acquisition cost of three of the most commonly used systemic therapies for posterior segment uveitis (prednisolone, mycophenolate mofetil and tacrolimus), shown in Table 29, vary widely. The recommended dose of prednisolone is 10 mg per day – doses higher than this would be avoided for long-term use because of the risk of AEs. Patients receiving prednisolone are also prescribed concomitant therapy with calcium and colecalciferol (Adcal D3) twice daily for bone protection and omeprazole for gastric protection. The annual costs of Adcal D3 and omeprazole have therefore been added to the annual cost of prednisolone.

Table 29 Annual cost of systemic prednisolone, mycophenolate mofetil, and tacrolimus in the treatment of posterior segment uveitis

Drug	Strength	Pack size	Pack cost (£)	Dose per day	Tablets per day	Drug cost per day (£)	Drug cost per year (£)
Prednisolone	5 mg	28	1.24	10 mg	2	0.089	95.16[a]
Mycophenolate mofetil	500 mg	50	9.31	2 g	4	0.74	271.85
Tacrolimus	1 mg	50	55.69	4 mg	4	4.46	1,626.15

[a]Including Adcal D3 (£47.58) and omeprazole 20 mg once daily (£15.25) concomitant therapy.
Drug costs are taken from the *British National Formulary*, July 2016 (55).

5.2.1 Cost of monitoring for comparators

Monitoring of patients taking systemic prednisolone, mycophenolate mofetil, or tacrolimus consists of outpatient visits for visual function testing to assess efficacy and to monitor AEs. Patients receiving a systemic corticosteroid or immunosuppressant receive a chest radiography and tuberculosis test before starting treatment. However, as all patients are likely to have been exposed to systemic corticosteroids before considering therapy with DEX 700, these costs are assumed to be incurred for all comparators and are not included here.

Patients on systemic prednisolone are monitored at baseline and weeks 4, 8, 14, 22, 30, 38, and 46, which is eight outpatient monitoring visits in the first year of therapy. Patients subsequently have an outpatient monitoring visit every 8 weeks if no problems were experienced on therapy. Therefore, the first year cost of monitoring for systemic prednisolone is £512 (£64 × 8), assuming that all monitoring costs are included in the cost of the follow-up outpatient visit tariff (53).

Patients on mycophenolate mofetil or tacrolimus are also monitored at baseline and weeks 4, 8, 14, 22, 30, 38, and 46 but also require an additional six monitoring visits for blood tests in the first year of therapy. Monitoring for these patients therefore comprises eight monitoring visits, costing £512 (£64 × 8), plus six blood test visits, costing £138 (£23 × 6); this assumes that the £23 cost for a non-face-to-face consultation reflects the cost of a visit for complete blood count and measurement of urea, electrolytes and liver function tests (53). Patients whose disease is well controlled after the first year of therapy then have a monitoring visit every 8 weeks (6.5 outpatient monitoring visits) and six additional non-face-to-face visits for blood tests.

5.2.2 Importance of monitoring costs for systemic therapies

The estimates for monitoring cost outlined above demonstrate the importance of considering cost components other than drug acquisition in the treatment of posterior segment uveitis. Systemic corticosteroids and immunosuppressants have low drug acquisition costs because generic versions of these older drugs are available. However, the annual cost of monitoring for toxicity is typically much greater than the annual drug acquisition cost. These hidden costs are often overlooked when focusing on the higher drug acquisition cost of DEX 700 compared with systemic therapy options.

5.3 Adverse event costs

It is difficult to estimate the costs of AEs with DEX 700 and comparators because of the lack of data to inform the modelling of events occurring over the long term. As outlined in Section 5.1.3, the highest mean cost of AEs associated with DEX 700 is likely to be for the treatment of raised IOP.

Zarranz-Ventura and colleagues (2014) reported that 42.5% of eyes treated with DEX 700 required IOP-lowering medication (among those for whom 12 month follow-up data were available) (15). The mean cost of treating this AE would be £59.72, assuming 12 months' continuous treatment (0.425 × £11.71 × 12). The proportion of patients with raised IOP was considerably lower in the HURON trial than in the real-world study reported by Zarranz-Ventura and colleagues, so the mean cost of £59.72 may be an overestimate.

It is difficult to estimate accurately the mean cost of AEs associated with the use of systemic prednisolone because no modelling estimates are available for the long-term cost in terms of increased osteoporosis, diabetes, and cardiovascular events that would be incurred with the long-term use of high-dose steroids in uveitis. It may be possible to estimate the costs of osteoporosis using the Sheffield Health Economic Model for Osteoporosis, as previously used in the modelling of corticosteroid-induced osteoporosis (56). This study estimated the risk of fractures for patients exposed to corticosteroids and the associated costs. Table 30 outlines the unit costs for fractures applied in the model.

Table 30 Unit costs for fractures applied in a cost–utility analysis of glucocorticoid-induced osteoporosis (56)

Age range (years)	Hip fracture	Vertebral fracture	Forearm fracture	Proximal humerus fracture
50–64	9,032	3,666	1,148	2,996
65–74	10,339			2,560
75-84	10,919			2,446
85+	15,672			2,350

Unit costs are in 2005 GBP.

Kanis and colleagues note that use of corticosteroids is not recorded consistently across studies assessing fracture risk, so the available data do not facilitate assessment of the reduction in fracture risk due to a reduction in the daily corticosteroid dose (56). Furthermore, data are not available for the increased fracture risk specifically in the population with posterior segment uveitis receiving systemic corticosteroids. Patients with posterior segment uveitis may be at increased risk of fracture due to systemic autoimmune conditions such as ankylosing spondylitis or rheumatoid arthritis, and are at increased risk of falls because of visual impairment.

The highest-cost AE associated with long-term use of systemic immunosuppressants is likely to be cases of malignancy. Yates and colleagues (2015) reported that, among 100 patients treated with systemic immunosuppressants and corticosteroids, an additional 1.67 malignancies would be observed per year compared with patients receiving systemic corticosteroids alone (see Section 4.4) (51). It is difficult to estimate the mean annual cost associated with this excess malignancy risk because of the range of malignancies involved. However, the most common malignancies were non-Hodgkin's lymphoma and non-melanoma skin cancer, so the cost can be expected to be substantial despite being 1.67 excess malignancies per 100 patient-years.

6 Implications for NHS resources

6.1 Prevalence of posterior segment uveitis

It is assumed that posterior segment uveitis represents 14% of all cases of non-infectious uveitis, based on estimates from Gritz and colleagues (2004) (6). Applying this proportion to the overall prevalence reported by Gritz et al (2004) gives an estimated prevalence of 16.14 per 100,000. The mid-2015 estimate for the adult population of England and Wales is 45,579,669 (57). Combining these estimates gives a prevalent population of 7,357 adults with posterior segment uveitis. This estimate is higher than the upper end of the range included in the NICE scope for this appraisal (5,000 patients) but is considered the most robust recent estimate for the prevalence of posterior segment uveitis in England and Wales.

6.2 Population eligible for treatment with DEX 700

It is estimated that 20% of the estimated 7,357 adults with posterior segment uveitis in England and Wales, will have sight-threatening disease that requires systemic therapy or DEX 700 (1,471 patients) (58). Systemic corticosteroids alone will achieve disease control in an estimated 60% (58) but the remaining 40% of patients will require further therapy (589 patients).

Few published estimates are available for the prevalence of unilateral and bilateral disease among patients with posterior segment uveitis. In the absence of alternative estimates of the proportion of patients with unilateral and bilateral disease, data from Zarranz-Ventura and colleagues (2014) for patients treated with DEX 700 in real world clinical practice have been applied. Zarranz-Ventura et al (2014) reported that 30.1% of patients treated with DEX 700 had bilateral disease (15). Therefore, it is assumed that 412 patients in England and Wales who are eligible for DEX 700 have unilateral disease and 177 have bilateral disease, giving a total of 589 eligible patients. Tomkins-Netzer and colleagues (2014) reported a slightly higher proportion of patients with bilateral disease (40.7%) (35). However, the estimates reported by Zarranz-Ventura and colleagues are preferred as they were from a larger study. Note that these studies only provide estimates of the proportion of patients receiving DEX 700 who have bilateral involvement. This is likely to be an underestimate of the proportion of all patients with posterior segment uveitis who have bilateral involvement if fewer bilateral affected patients were selected to receive DEX 700 therapy. Nevertheless, these studies provide appropriate estimates of how many patients have bilateral disease in those selected for DEX 700 therapy.

6.3 Budget impact model

A budget impact model was constructed in Microsoft Excel® using the eligible patient population of 589 patients estimated in Section 6.2. The model is prevalence based and assumes a constant patient population (i.e., incidence and mortality are not accounted for in the model).

6.3.1 Monitoring and administration costs

The model uses the cost estimates outlined in Section 5. DEX 700 is assumed to be administered during an outpatient visit to an ophthalmology clinic for a minor vitreous procedure. No administration costs are assumed for the systemic therapy options. Cost inputs differ for the first

year of therapy, when more intensive monitoring is required compared with subsequent years. Table 31 outlines the unit costs and resource use used as inputs in the model.

Table 31 Unit costs and resource use used as inputs for the budget impact model

Item	Input
DEX 700 injection visit	£109
Follow-up outpatient ophthalmology monitoring visit	£64
Blood monitoring visit (non-face-to-face outpatient visit)	£23
Mean implants per year	
Unilateral	1.64
Bilateral	3.28
Mean injection visits	
Unilateral	1.64
Bilateral	3.28
Mean outpatient monitoring visits	4.92
Mean prednisolone outpatient monitoring visits	
year 1	8
Subsequent years	6.5
Mycophenolate mofetil/tacrolimus monitoring	
Mean outpatient monitoring visits, year 1	8
Mean outpatient monitoring visits, subsequent years	6.5
Mean visits for blood monitoring per year	6

Details of the calculations for the number of visits required for each therapy are provided in Section 5.

6.3.2 Drug acquisition costs

The drug acquisition costs applied in the model have been calculated using prices in the British National Formulary (55). It is assumed based on expert opinion (NHS consultant ophthalmologist, personal communication) that the mean daily dose of mycophenolate mofetil is 2 g and the mean daily dose of tacrolimus is 4 mg. A dose of 10 mg of prednisolone has been used, as this is likely to be the maximum long-term maintenance dose that would be considered (alternative treatment options would be considered for patients requiring higher doses for control of their disease). Drug acquisition costs are set out in Table 32.

Table 32 Drug acquisition costs used in the budget impact model

Drug	Strength	Pack size	Pack cost (£)	Dose per day	Tablets per day	Cost per day (£)	Cost per year (£)
DEX 700 implant, unilateral	–	–	870	–	–	–	1,426.80
DEX 700 implant, bilateral	–	–	870	–	–	–	2,853.60
Prednisolone	5 mg	28	1.24	10 mg	2	0.089	95.16
Mycophenolate mofetil	500 mg	50	9.31	2 g	4	0.74	271.85
Tacrolimus	1 mg	50	55.69	4 mg	4	4.46	1,626.15

[a]Including Adcal D3 (£47.58) and omeprazole 20 mg once daily (£15.25) concomitant therapy.
Drug costs are taken from the *British National Formulary*, July 2016 (55).

6.3.3 Annual costs per patient

The annual cost of DEX 700 implants has been calculated based on the mean number of treatments reported by Zarranz-Ventura and colleagues (2014) for all patients with 12 months' follow-up data (15). This estimate accounts for patients whose symptoms were controlled with only one implant per year, and those who received further implants before or after 6 months. Patients with unilateral disease required, on average, 1.64 implants per year. For patients with bilateral disease this is assumed to be doubled (3.28 implants per year).

Estimated drug costs, monitoring and administration costs, and total costs of therapy for the first year of treatment are presented in Table 33. Costs are higher in the first year because of greater monitoring requirements. Costs for DEX 700 are based on 30.1% of patients receiving bilateral treatment (15).

Table 33 Drug acquisition and monitoring and administration costs, and total costs per patient in year 1

	Drug costs	Monitoring and administration costs	Total cost
Unilateral DEX 700	£1,427	£494	£1,920
Bilateral DEX 700	£2,854	£672	£3,526
Total DEX 700 (30.1% bilateral)	£1,856	£547	£2,404
Prednisolone	£95	£416	£574
Mycophenolate mofetil	£272	£554	£826
Tacrolimus	£1,626	£554	£2,180

The costs in Table 33 highlight the high proportion of the total costs for systemic corticosteroids and systemic immunosuppressants that are attributable to monitoring requirements. The annual cost of prednisolone is lower for than other therapies. Tacrolimus and bilateral DEX 700 are the highest cost therapies.

6.3.4 Annual costs for treating the eligible patient cohort

Table 34 shows the first year's cost of treatment and Table 35 shows the subsequent years' cost of treatment for the estimated 589 patients eligible for DEX 700 therapy. It was assumed that 69.9% of patients are treated with DEX 700 in one eye and 30.1% in both eyes, as described above.

Table 34 Total costs for the eligible population for DEX 700 in England and Wales (n = 589) in year 1

Cohort year 1	Drug costs	Monitoring and administration costs	Total cost
DEX 700	£1,092,929	£322,394	£1,415,323
Prednisolone	£56,050	£301,568	£357,618
Mycophenolate mofetil	£160,121	£382,850	£542,971
Tacrolimus	£957,801	£382,850	£1,340,651

Table 35 Total costs for the eligible population for DEX 700 in England and Wales (n = 589) after year 1

Cohort year 2 or more	Drug costs	Monitoring and administration costs	Total cost
DEX 700	£1,092,929	£322,394	£1,415,323
Prednisolone	£56,050	£245,024	£301,074
Mycophenolate mofetil	£160,121	£326,306	£486,427
Tacrolimus	£957,801	£326,306	£1,284,107

6.3.5 Cumulative 5 year costs of treatment

Table 36 to Table 39 give the cumulative costs of treatment over a 5 year period for each of the therapy options if all patients in the eligible cohort are treated with that therapy.

Table 36 Cumulative 5 year costs of treating 589 eligible patients with DEX 700

Year	Drug costs	Monitoring and administration costs	Total cost
1	£1,092,929	£322,394	£1,415,323
2	£2,185,858	£644,789	£2,830,647
3	£3,278,786	£967,183	£4,245,970
4	£4,371,715	£1,289,578	£5,661,293
5	£5,464,644	£1,611,972	£7,076,616

Table 37 Cumulative 5-year costs of treating 589 eligible patients with prednisolone

Year	Drug costs	Monitoring and administration costs	Total cost
1	£56,050	£301,568	£357,618
2	£112,099	£546,592	£658,691
3	£168,149	£791,616	£959,765
4	£224,199	£1,036,640	£1,260,839
5	£280,248	£1,281,664	£1,561,912

Table 38 Cumulative 5 year costs of treating 589 eligible patients with mycophenolate mofetil

Year	Drug costs	Monitoring and administration costs	Total cost
1	£160,121	£382,850	£542,971
2	£320,242	£709,156	£1,029,398
3	£480,362	£1,035,462	£1,515,824
4	£640,483	£1,361,768	£2,002,251
5	£800,604	£1,688,074	£2,488,678

Table 39 Cumulative 5 year costs of treating 589 eligible patients with tacrolimus

Year	Drug costs	Monitoring and administration costs	Total cost
1	£957,801	£382,850	£1,340,651
2	£1,915,602	£709,156	£2,624,758
3	£2,873,404	£1,035,462	£3,908,866
4	£3,831,205	£1,361,768	£5,192,973
5	£4,789,006	£1,688,074	£6,477,080

6.3.6 Net budget impact over 5 years for DEX 700 vs comparators

The model also calculates the net budget impact of DEX 700 compared with each of the comparators. These analyses compared cumulative treatment costs assuming that all patients receive DEX 700 rather than prednisolone, mycophenolate mofetil, or tacrolimus. Table 40 to Table 42 present the cumulative cost differences over the 5 year period.

Table 40 Net cumulative budget impact of treating all patients in the eligible population with DEX 700 rather than prednisolone

Year	Drug costs	Monitoring and administration costs	Total cost
1	£1,036,879	£20,826	£1,057,706
2	£2,073,758	£98,197	£2,171,955
3	£3,110,637	£175,567	£3,286,205
4	£4,147,517	£252,938	£4,400,454
5	£5,184,396	£330,308	£5,514,704

Table 41 Net cumulative budget impact of treating all patients in the eligible population with DEX 700 rather than mycophenolate mofetil

Year	Drug costs	Monitoring and administration costs	Total cost
1	£932,808	−£60,456	£872,352
2	£1,865,616	−£64,367	£1,801,249
3	£2,798,424	−£68,279	£2,730,145
4	£3,731,232	−£72,190	£3,659,042
5	£4,664,040	−£76,102	£4,587,938

Table 42 Net cumulative budget impact of treating all patients in the eligible population with DEX 700 rather than tacrolimus

Year	Drug costs	Monitoring and administration costs	Total cost
1	£135,128	−£60,456	£74,672
2	£270,255	−£64,367	£205,888
3	£405,383	−£68,279	£337,104
4	£540,511	−£72,190	£468,320
5	£675,638	−£76,102	£599,537

6.3.7 Conclusions and limitations of the model

These estimates indicate that treating all eligible patients with DEX 700 rather than continuing on 10 mg systemic prednisolone would result in an increased cost of £5.5 million over 5 years. Treating all eligible patients with DEX 700 rather than mycophenolate mofetil would result in an increased cost of £4.6 million over 5 years, and treating all eligible patients with DEX 700 rather than tacrolimus would result in an increased cost of £599,537 over 5 years. The results show that the higher drug acquisition costs of DEX 700 are partially offset by savings in reduced monitoring costs with intravitreal DEX 700 therapy compared these systemic therapy options. However, this does not include the cost offsets that would potentially be realised through a reduction in the adverse effects of long-term treatment with systemic corticosteroids and immunosuppressants, which are likely to be substantial but are difficult to estimate.

These analyses have a number of limitations. Firstly, limited data are available to ascertain the likely proportion of patients eligible for DEX 700 who would require bilateral treatment. The budget impact estimates indicate the maximum difference in the costs of treatment over 5 years assuming all patients receive *one* of the therapy options. A more accurate estimate of the net budget impact would require information on the market shares of all likely therapy options at baseline and which therapies would be most likely to be displaced by the introduction of DEX 700.

It should also be noted that therapies would typically be considered for add on, and the baseline dose of existing therapies would be reduced in patients who are treated successfully, as outlined in the clinical studies with DEX 700 detailed in Section 2.6.

A further limitation of the analyses is that costs of AEs have not been included. As noted in Section 5, the cost of treating the AEs of systemic corticosteroids and immunosuppressants may be significant, particularly if high doses are required. The analysis assumes the same maintenance doses of therapy

over time, in the absence of data relating to dose requirements in the long-term use of DEX 700 and comparators in the treatment of posterior segment uveitis. The budget impact model focuses on use of DEX 700 as a long-term maintenance therapy option. DEX 700 is also an alternative to the use of high-dose systemic therapy in the acute phase of the disease.

7 Equality implications

Although a rare condition, posterior segment uveitis is one of the main causes of vision loss in working-age adults. The equality impact of recommendations for those patients for whom vision may be reduced or lost in one eye already may need to be assessed, as this group is at risk of becoming sight disabled.

8 Abbreviations

AE	adverse event
ANOVA	analysis of variance
AREDS	Age Related Eye Disease Study Research Group
BCVA	best corrected visual acuity
BRVO	branch retinal vein occlusion
CI	confidence intervals
CRT	central retinal thickness
CRVO	central retinal vein occlusion
DEX 700	700 µg dexamethasone intravitreal implant (OZURDEX)
DMO	diabetic macular oedema
EMA	European Medicines Agency
EQ VAS	visual analogue scale for eliciting a self-rating of health status
EQ-5D	EuroQol five-dimension questionnaire
ETDRS	Early Treatment of Diabetic Retinopathy Study
GPRD	General Practice Research Database
HIV	human immunodeficiency virus
HR	hazard ratio
HRQL	health-related qualify of life
IOP	intraocular pressure
IQR	interquartile range
ITT	intent-to-treat
LOCF	last observation carried forward
MTA	multiple technology appraisal
MUST	Multicentre Uveitis Steroid Treatment
NEI	National Eye Institute
NHMS	National Health Measurement Survey
NHS	National Health Service
OCT	optical coherence tomography
PP	per protocol
PPV	pars plana vitrectomy
PS DDS	Posterior Segment Drug Delivery System
RCT	randomised controlled trial
RVO	retinal vein occlusion
SD	standard deviation
SE	standard error
SEM	standard error of the mean

SF-36	short-form 36 questionnaire
SF-6D	short-form six-dimension questionnaire
SPC	summary of product characteristics
TNF	tumour necrosis factor
VA	visual acuity
VAS	visual analogue scale
VFQ	Visual Function Questionnaire

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation statement (MTA) Adalimumab and dexamethasone for treating non-infectious uveitis [ID763]

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment(s).

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to say which treatment (s) you are commenting on.

1. About you and your organisation

Your name: [redacted]
Name of your organisation: Birdshot Uveitis Society (BUS)
Your position in the organisation: [redacted]
Brief description of the organisation:
(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Birdshot Uveitis Society (BUS) is a small charity and support group for people with the rare, hard to treat autoimmune posterior uveitis called Birdshot Chorioretinopathy or Birdshot Uveitis. BUS was founded in 2009 by two patients who both have Birdshot. It was granted charitable status in 2011, and depends on donations and fundraising by its members. BUS is run by unpaid volunteers who either have Birdshot or who have a family member with it.

There are over 500 people registered with BUS. Membership is worldwide, but primarily from the UK. As well as people with Birdshot, membership includes healthcare professionals and others with an interest in Birdshot. BUS has set up a National Birdshot Research Network. Working with this network, BUS has helped to establish a National Birdshot Database and Bio-resource Centre in Birmingham to provide a foundation for future Birdshot research.

Links with, or funding from the tobacco industry – please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Birdshot uveitis is bilateral, usually painless, progressive and potentially blinding. The initial symptoms are usually floaters and/or blurred vision caused by the presence of inflammatory cells in the vitreous. Other symptoms may include night blindness, impaired vision in low light, delayed light/dark adaptation, defective colour vision, sensitivity to bright lights or glare, a perception of flickering or flashing lights, fluctuating vision, decreased ability to perceive depth, shimmering vision, distorted images and decreased peripheral vision.

These effects on vision affect, often profoundly, the ability of Birdshot patients to perform many activities of daily living and to continue in work or education.

Before being diagnosed with Birdshot, patients have considerable anxieties over what is going wrong with their vision. Once diagnosed, other concerns include fear of the possibility of blindness, of not being able to continue to work or to drive, of not being able to see one's children grow up, and of losing one's independence. As a

result, patients frequently suffer problems with depression and anxiety, often worsened by the considerable burden of side-effects from the commonly prescribed medications used to treat Birdshot.

Currently used treatments are often not well tolerated. Some medications need to be taken at specific times in relation to meals, leading to a daily life governed by taking medication. Frequent clinic visits for treatment monitoring and vision checks disrupt life and work for all Birdshot patients and their families. Clinic vision checks usually require the eyes to be dilated for examination. This means that the patient cannot drive themselves to and from their appointments and may also need to be accompanied. After eye dilation, patients are likely not to be able to see well enough to resume work, necessitating taking the whole day off.

Families, friends and employers often find it hard to understand that Birdshot patients have a real problem with their sight. It is common for relatives to be in denial about Birdshot because they simply do not appreciate the visual problems that patients experience. They also find it hard to understand that changes in behaviour may be more to do with medication taken for Birdshot, particularly oral corticosteroids, than for any other reason.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Above all, Birdshot patients want to have treatment which controls their condition and keeps it under control, and which preserves and improves their vision with minimal impact on their physical and mental health, allowing them to work and carry on their lives as normal.

Patients want to have a realistic prospect of receiving treatments which will achieve the goals of attaining a state of clinical remission of disease activity, preferably on no or minimal corticosteroids, then being able to taper and stop treatment, with continued monitoring to check that remission is maintained.

In practice, with current treatments and the considerable adverse effects that they can all cause, these goals are notoriously difficult to achieve without the uveitis flaring, often many times, leading to the common ‘Birdshot rollercoaster’ treatment experience.

Patients would also prefer not to have their lives revolve around frequent hospital appointments for treatment and monitoring.

In summary, the most important treatment outcomes that both patients and carers want to achieve are:

- control of inflammation;
- maintenance of good visual function;
- minimal treatment-related side-effects;
- and a reduction in the number of hospital eye clinic visits.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these different treatments and which are preferred and why?

Currently available NHS care for Birdshot patients is usually provided in specialised uveitis clinics in tertiary hospitals. Diagnosis can be difficult. Because the condition is rare, there may be delays (years in some cases) in patients reaching specialist uveitis care, during which time their Birdshot has continued to progress, adding to the difficulties of getting it under control.

Current treatment principles for Birdshot are to use high doses of corticosteroid (usually orally but sometimes by injection into the eye) to control the inflammation, then to introduce one or more oral (or occasionally injectable) immunosuppressants as second-line agents to modify the underlying immune dysfunction which is attacking the eye tissues. The oral corticosteroid dose is then slowly tapered with a view to stopping it. In practice, lowering the corticosteroid dose without inducing a disease flare can be very difficult. Many patients have to remain on quite high maintenance corticosteroid doses.

Long term use of high-dose oral corticosteroids causes numerous health problems. These include weight gain, fluid retention, osteoporosis and diabetes. Anger, irritability and depression are frequent complaints. Insomnia, restlessness, and unreasonable behaviour, plus tiredness and lack of concentration because of the insomnia, are so common as to be considered normal consequences of high-dose corticosteroids. Persistent stomach pain may require medication. Continued use of corticosteroids can lead to cataract development, which further worsens sight and necessitates lens replacement surgery. Raised intraocular pressure caused by corticosteroids requires eyedrop or oral treatments or possibly surgery.

Immunosuppressants used with corticosteroids as second-line treatment for Birdshot include azathioprine, ciclosporin, methotrexate, mycophenolate mofetil and tacrolimus.

All these immunosuppressants have considerable side-effect profiles. The most common are stomach pain, nausea, vomiting and diarrhoea. Specific immunosuppressants can cause alterations to liver, kidney or bone marrow function, which may mean that treatment has to be stopped and another immunosuppressant tried. Raised blood pressure and raised cholesterol caused by certain immunosuppressants require more medication for control. Suppressing the immune system means that patients are more liable to pick up infections which may not develop as normal. Common immunosuppressant side-effects include fatigue, insomnia, depression, joint and muscle aches and pains, 'pins and needles', tremor, hair thinning, excess body hair and overgrowth of gum tissue. The cumulative impact of these side effects is compounded by the frequent need for more than one immunosuppressant to be used, often alongside large doses of corticosteroids.

The consequence of no treatment is progressive sight loss. None of the current treatments can be stated as being 'preferred'. Several treatment changes may be needed to find a regime which can be tolerated and which can also be shown to work adequately.

This is why better targeted medicinal products need to become part of the Birdshot treatment armoury. It is also the reason why non-systemic treatments such as implants provide attractive alternatives to current systemic treatments, and also why adalimumab, a biologic anti-TNF-α (anti-tumour necrosis factor) targeted immune modulator, needs to be available to treat severe or difficult cases of posterior uveitis, including Birdshot.

4. What do patients or carers consider to be the advantages of the treatment(s) being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment(s) being appraised.

Both treatments: simplification and potential improvement of treatment by elimination or reduction of daily oral medication and its side-effects.

Adalimumab: of particular benefit for patients who either cannot tolerate the currently used immunosuppressant medications or who have shown an inadequate response to them. Self-injection every two weeks, rather than daily oral medication-taking, encourages better treatment compliance as well as improved quality of life.

Dexamethasone intravitreal implant: treating the eye rather than the whole body, leading to better health and quality of life.

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England.

Replies in this section are from patient questionnaires completed by BUS members.

Adalimumab: improved vision. Stable vision. Able to reduce oral corticosteroids successfully. Ease of use – self-injection every two weeks. No or minimal oral medicines, thus eliminating or reducing medication side-effects. Feeling well – better than when on oral medication. More energy. More confidence in wellbeing. Positive outlook on life.

“Little short of instantaneously fantastic [effect on vision].”

“Controls the disease without making me ill, so I can work and enjoy life.”

“Before adalimumab, the world was disappearing in front of me, and so rapidly. Now I can see again, clearly, and it is wonderful.”

“Since starting adalimumab, I have managed to gradually reduce prednisolone successfully...I am now on only 2mg daily.”

“All other medication wasn’t working. If it wasn’t for adalimumab, I don’t know or would like to think [about] where I would be now.”

Dexamethasone intravitreal implant: quick procedure. Quick improvement in vision. Not having to take oral corticosteroids. Clearer sight. No constant reminders of Birdshot through taking oral corticosteroids. Gastric inflammation gone. Feeling well. Night blindness improved. Less light needed when reading.

“Gave me vision I have not had in 10 years.”

“When everything else has been tried and nothing is working, this implant has saved my sight that is at risk from constant flares of inflammation.”

Comment received by BUS from patient using adalimumab and who has also had dexamethasone intravitreal implant:
“[Both] treatments have worked wonders for me. [Adalimumab] self-injection has helped keep my condition under better control, with no side-effects to concern [me] nor stop me going about my daily business. [Dexamethasone intravitreal implant insertion] went smoothly and with little discomfort. After a couple of days, I was absolutely pleasantly impressed with my vision. I could not stop smiling for weeks. I would truly recommend [these] treatments.”

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

Replies in this section are from patient questionnaires completed by BUS members.

Adalimumab: quick improvement for some patients versus slow and steady improvement for others.

Dexamethasone intravitreal implant: most patients reported good outcomes but over differing periods of time - on average 3 to 6 months - with one or two cases where the treatment did not work and the corticosteroid dissipated almost immediately.

5. What do patients and/or carers consider to be the disadvantages of the treatment(s) being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse

- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

No medications are licensed for use in Birdshot. When the small range of treatments currently available for Birdshot either does not work, or makes patients so ill that treatment has to be stopped, they would prefer that their clinicians and BUS did not have to spend valuable time battling the authorities for permission to use newer treatments. The prospect of sight loss is daunting enough for patients without the additional upset of being told that a possible treatment cannot be used because it is not yet approved for use or because of its cost. It is inequitable and unjust that newer treatments which have been used successfully in other countries are not available to Birdshot patients in England.

Patients are concerned that the current systemic treatments available for Birdshot, particularly long-term oral corticosteroids, come with considerable side-effects. Usually, patients are otherwise healthy when they are diagnosed with Birdshot. Although the medications are prescribed to save vision, treatment can profoundly affect Birdshot patients' health and quality of life. Patients suddenly find that, as well as the medication that they need to take for their eyes, they have to take additional medications for drug-induced side-effects. These medications, in turn, have further side effects.

Some BUS members have reported feeling so unwell on treatment that they have considered discontinuing it and letting their Birdshot take its course towards blindness.

Issues of greatest concern from current treatments are:

- Long term use of high-dose oral corticosteroids causing numerous health problems, including weight gain; fluid retention; gastric problems; osteoporosis; diabetes; anger; irritability and depression; insomnia; restlessness and unreasonable behaviour; tiredness and lack of concentration because of the insomnia.

- Side effects from the use of immunosuppressant medication include: increased risk of infections; prolonged infections; increased skin cancer risk;

gastric problems such as vomiting, diarrhoea and stomach pain; blood pressure and cholesterol issues; excessive growth of hair; loss of hair.

- For women and men who wish to have a family, it may be unsafe to do so while on immunosuppressive treatment.

Please list any concerns patients or carers have about the treatment(s) being appraised.

Adalimumab: concerns raised by patients about giving own injections; pain on injection; long-term side-effects not known; fear that initial benefits may not be sustained.

Dexamethasone intravitreal implant: hospital insertion procedure which needs to be repeated every few months. Only one eye is usually treated at a time. Recovery time from each procedure reduces the amount of patient benefit time available before the next treatment is required. Other concerns raised by patients include: whether the treatment is only controlling the symptoms but not the underlying disease; how long each treatment will last; whether there is a risk from repeated treatments; whether the eye will be bloodshot or painful.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

Replies in this section are from patient questionnaires completed by BUS members.

Adalimumab: pain on injection versus less pain if injection is at room temperature.

Dexamethasone intravitreal implant: minimal discomfort on insertion versus pain, headache and nausea on insertion.

6. Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others? If so, please describe them and explain why.

Of all non-infectious posterior uveitis patients, those with Birdshot are particularly suitable for local therapies such as dexamethasone intravitreal implant because the inflammation appears to be localised purely in the eye.

Adalimumab: patients whose vision is deteriorating because of continuing inflammation or who are unable to tolerate the traditional second-line immunosuppressants, because adalimumab targets the immune system dysfunction differently from conventional immunosuppressants. Its injectable route eliminates the gastrointestinal side-effects of oral treatments.

Dexamethasone intravitreal implant: patients who are unable to reduce their doses of oral corticosteroids without their Birdshot flaring, particularly patients with persistent cystoid macular oedema.

Are there any groups of patients who might benefit less from the treatment(s) than others? If so, please describe them and explain why.

Patients with a phobia of needles.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment(s)?

☑ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment(s) as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Adalimumab: patient experience, for those who have secured individual funding requests in the past for NHS use in England, or who live in Scotland, reflects patient experience in the trials accessed.

Dexamethasone intravitreal implant: a) Birdshot patient experience can involve repeated insertions every six months, probably into both eyes, and the HURON trial studied single insertions into one eye only; b) patient experience reflects use of dexamethasone intravitreal implant as an alternative to oral corticosteroids, but some HURON triallists continued taking oral doses of corticosteroid equivalent to 20mg/day or less of prednisolone.

See also Section 4 (advantages described by patients) and Section 5 (patient concerns).

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

a) Outcomes:
All major trials accessed for both treatments used the National Eye Institute Visual Function Questionnaire-25 (VFQ-25) to measure patient-reported aspects of vision-related functioning over the trial duration. VFQ-25 gives a much better measure of important aspects of day-to-day vision and vision-related quality of life than the standard clinic eye test of best-corrected visual acuity (BCVA).

b) Limitations:
i) For both treatments: 'posterior uveitis' is not a single medical condition. Trials accessed included patients with a number of different types of posterior uveitis which have different underlying causes. Because Birdshot is an officially rare condition, only small numbers of Birdshot patients have been included in trials of treatments for

posterior uveitis. This makes it difficult to assess the relevance of clinical trials information to a wider population of Birdshot patients.
ii) Duration: many trials were short. Birdshot is a chronic condition.
iii) Exclusions: many posterior uveitis patients were judged 'atypical' and not included in trials.
iv) Trial patient populations: may not represent the full spectrum of ages, presentations of posterior uveitis and the co-morbidities of patients seen in clinical practice.
v) Trial designs: many trial types and sizes, making comparisons difficult.
vi) Observer bias in measuring trial outcomes: lack of objective methods which would make trials easier to compare.

If already available in the NHS, are there any side effects associated with treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

Dexamethasone intravitreal implant: more cases of raised intraocular pressure post-insertion noted in practice (Zarrans-Ventura *et al;* 2014) than in the HURON study. See also Section 5 (patient concerns about the treatments being appraised).

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☑ Yes ☐ No

If yes, please provide references to the relevant studies.

1. Koutroumanos N, Folkard A, Mattocks R *et al.* Bringing together patient and specialists: the first Birdshot Day. *British Journal of Ophthalmology* 2013 May; 97 (5): 648-52. doi: 10.1136/bjophthalmol-2012-302134

2. Barry JA, Folkard A, Denniston AK *et al.* Development and validation of quality – of-life questionnaires for birdshot chorioretinopathy. *Ophthalmology* 2014 Jul; 121 (7): 1488-9. e2. doi:10.1016/j.ophtha.2014.01.007

3. Barry JA, Folkard A & Ayliffe W. Validation of a brief questionnaire measuring positive mindset in patients with uveitis. *Psychology, Community & Health,* 2014; 3 (1): 1-10. doi:10.5964/pch.v3i1.76

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Both treatments are already approved for use in suitable patients in Scotland who have non-infectious posterior uveitis, including Birdshot. Patients in England are currently denied this medication: inequality based on country of residence, not clinical need.

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Adalimumab: self-injection might be a problem for some patients.

9. Other issues

Do you consider the treatment(s) being appraised to be innovative?

☑ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

Adalimumab: significantly different treatment because it is a targeted anti-TNF-α biologic systemic medication which regulates the underlying immune system dysfunction in Birdshot.

Dexamethasone intravitreal implant: treating the eye rather than the whole body. Designed as a slow-release, long-acting corticosteroid, it is the first intravitreal treatment licensed for treating uveitis.

Are there any other issues that you would like the Appraisal Committee to consider?

Why were other anti-TNF-α medications already in use for treating severe refractory posterior uveitis, eg, infliximab (Remicade) and other intravitreal corticosteroids, eg, fluocinolone acetonide 0.18mg implant (Iluvien) not used as comparators in this appraisal?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Current treatments may not control Birdshot uveitis
- Current Birdshot treatments cause a considerable burden of mental and physical side-effects
- Wider range of better targeted treatments is needed to preserve and improve vision
- Adalimumab injection has already benefited Birdshot patients in other countries, including Scotland, who either cannot tolerate, or who have not responded to conventional immunosuppressants, and it should be made available for use in England
- Dexamethasone intravitreal implant, also available in Scotland for treating posterior uveitis, avoids the considerable side-effects of conventional systemic corticosteroids, and it should be made available for Birdshot patients in England

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (MTA)

Adalimumab, dexamethasone and sirolimus for treating non-infectious uveitis

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment(s).

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to say which treatment (s) you are commenting on.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Olivia's Vision

Your position in the organisation: [redacted]

Brief description of the organisation: The charity seeks to educate patients and carers about uveitis, support patients and carers through treatment, raise funds for research into uveitis, fund and provide Fellowship training in uveitis, fund and provide training of specialist nurses.

The charity is small – 3 Trustees and 1 volunteer. Funds come from the fund raising of supporters and the Trustees.

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Living with the condition is upsetting and frightening especially when uveitis is chronic and sight threatening. Vision can be lost quickly and sometimes cannot be recovered. When existing therapies do work to reduce disease activity, the therapy itself can be unpleasant and debilitating and cause patients to make life style changes. The path to effective therapy is not always a straight path with patients having to adjust to increased doses of their drugs and changes of therapy until an effective drug, or combination of drugs, results in drug induced remission. Patients feel worn down when they comply

with their treatment protocols yet their eyes still flare. For some patients, appointments may become an accumulation of disasters once the complications of uveitis set in with the management of these creating constant worry. Patients develop cataracts which compromise their vision, they may require management of their high ocular pressure and cystoid macular oedema is especially debilitating since reading may be difficult and driving stopped.

The fact that there is no cure and the open ended duration of therapy are both difficult. Alongside this, some patients with idiopathic disease worry excessively about cause and want an explanation of why they have uveitis. Many patients are relieved to find support groups on the internet and charities, such as Olivia's Vision, providing information, education about the condition and support. Not many clinics run patient groups which provide education and the opportunity to meet others living with the disease, so it is common for patients to feel isolated. Patients don't always understand their disease, they panic when abnormal blood test results mean they have to stop a therapy for a week and few in their immediate social circle understand their anxiety. Uveitis is a lonely disease.

Patients with severe disease become depressed, especially when they have fluctuations in vision and experience pain. Attendance at eye clinics can take up a lot of time and not all employers are sympathetic and supportive. Throughout all of this, the greatest fear of patients is that they will become blind. For those for whom the disease remains refractory on existing therapy, life is miserable.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

The most important outcome for patients is the preservation of their vision. The loss of this is what they fear most.

Patients want their treatments to stop their intraocular inflammation.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these different treatments and which are preferred and why?

NHS care typically follows treatment guidelines.

Patients begin with corticosteroid in various forms. When drops are required, the frequency of instilling these may take over patients' lives. High dose oral pills are almost universally disliked with the main complaints being weight gain and changes to mood. Iv infusions are better tolerated. Sub tenon injections can cause ptosis and one patient has told us corrective surgery, funded by this patient, was needed. Patients have the distress of cataract formation and surgery for this. Some patients require glaucoma surgery when ocular pressure cannot be medically managed.

Conventional immune suppressants generally cause patients to feel tired and pose problems with increased susceptibility to infection. Specific problems reported to us are as follows:

Methotrexate – tiredness, thinning of hair, nausea, problems with liver function.

Ciclosporin – problems with the urinary tract and kidneys. Sleep affected. Female patients dislike becoming hirsute.

Mycophenolate mofetil – night sweats, tiredness, nausea.

Azathioprine – problems with nausea and liver function.

Tacrolimus – not many patients receive this but those who do state they tolerate it better than ciclosporin.

Patients react to immune suppressants in different ways and preference is individual.

4. What do patients or carers consider to be the advantages of the treatment(s) being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment(s) being appraised.

Adalimumab –

Ease of use at home fortnightly

Inflammation brought under control

Cystoid macular oedema resolved, then prevented

Prevention of other damage to tissue and structures in the eye

Improvement, or no further worsening, in visual acuity

Release from constant anxiety about sight and thus improved mental health

The provision of a period free from inflammation necessary before ocular surgery (cataract, glaucoma, vitrectomy) and prevention of post-operative inflammation

The possibility of sight being recovered

When sight does improve, increase in independence, the ability to return to work, reduction in time off to attend appointments

Possibility of dropping one or two immune suppressants and their side effects

Improved quality of life

When patient and specialist are comfortable with the risk, the possibility of pregnancy

For some, the ability to drive, to read, to continue education or training and to work, allowing the patient to be a productive member of society and to provide for a family.

Once disease has been controlled, the frequency of monitoring in clinic is reduced benefitting both patient and hospital.

Dexamethasone implant

Systemic side effects of high dose oral steroid avoided

Quick reduction in disease activity may occur

Potential for reduced need of concomitant therapy

Implant effective for three months and longer

Mental health improves when a flare up is controlled

If vision improves, so does quality of life

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England.

For both therapies, the advantages for patients are better control of their condition, the possibility that lost vision may be recovered, both therapies are easier to manage than daily or weekly pills and the reduction in the side effects of existing oral therapies.

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

Patients with unilateral disease and no underlying condition may prefer the dexamethasone implant. Some patients and carers may prefer it because the patient does not have to take pills daily, eat at certain times, avoid alcohol and when the implant is effective as monotherapy, the risk of potentially serious side effects associated with immune suppressants and biologic therapy are avoided. The implant may have additional advantages for young people taking control of their treatment for the first time as they transition to adult care. Carers of these young people may have their anxiety reduced that their now grown up child will not comply with treatment protocols or become unintentionally pregnant, especially when the young person moves away from home to study or work. For those wishing to start families, the implant may appeal as safer than biologic therapy. Patients who travel constantly for work do not have to worry about taking medication which requires refrigeration with them.

Patients with bi-lateral disease may prefer adalimumab to implants in both eyes, especially if they are steroid responders. Some patients believe that steroid does not change the action of the immune system and therefore, therapy with implants will continue for many years with all the risks associated with injections into the eye repeated many times. Some patients hope that therapy with immune suppressants or biologic therapy can be successfully stopped after two years of drug induced remission and their eyes will stay inflammation free.

5. What do patients and/or carers consider to be the disadvantages of the treatment(s) being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)

- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)

Disadvantages of dexamethasone implants.

The need for repeated injections.

The variation in length of clinical effect. Patients tell us their implants are clinically effective for three to twelve months before symptoms tell them they have inflammation. It may be that patients are not actually reporting how long their implants work because the periods they report between implants may include periods of natural remission from inflammatory activity, rather than steroid induced periods of remission.

The implant may have insufficient clinical effectiveness when used as monotherapy. Some patients have told us they also use an immune suppressant and the implant is given when they have inflammation. One bi-lateral idiopathic pan uveitis patient said mycophenolate mofetil, begun about a year ago, has helped a lot. Previously, the patient needed an implant every 5-6 months. She is having an implant this week in one eye, a year after the eye's last implant. Over the past three years, this patient has had a total of 9 implants for her eyes. This patient cannot raise her dose of mycophenolate to the level her ophthalmologist considers would be optimal because the tiredness and sickness mean she struggles to go to work.

Most patients report discomfort when they receive their implants and some dislike the subconjunctival haemorrhages which sometimes occur. They are happy to tolerate these things because of the benefit, fewer flare ups of disease activity, received.

Time off work and attendance at a clinic to receive the implant are a problem for some patients. Some make up time missed at work.

Single parents with young children who have to travel a significant distance to a specialist's clinic must fund child care, as well as travel costs, to receive their treatment.

The development of cataract and risk of raised ocular pressure. For the patient with unilateral disease, cataract surgery may result in a difference of prescription between the eyes which the patient cannot accommodate.

Disadvantages of adalimumab.

The time taken for clinical effectiveness to build up. Patients tell us they wait between eight and twelve weeks before clinical benefit is apparent either through examination in clinic or through improved vision.

A few patients may need weekly rather than fortnightly injections.

The potential for serious side effects, particularly the risks of lymphoma and leukaemia, scare some patients.

Better read patients are aware that MS may develop. However, specialists are unlikely to offer this therapy when they suspect their patient's uveitis is the presenting symptom of MS. One patient told us she had an MRI, with a lumber puncture also considered, before beginning treatment with adalimumab.

Irritation at the site of injection.

A few patients have told us they feel a little unwell and tired after their injections. These same patients say that these side effects of adalimumab are less debilitating than those they experienced with conventional immune suppressants.

The risk of serious infections and the need for respiratory infections to be monitored in case pneumonia or sepsis develop.

Please list any concerns patients or carers have about current NHS treatments in England.

Amongst those who have already lost vision and who are failing immune suppressant therapy, there are serious concerns about the lack of effective therapy available to them. Some of these patients are suffering badly and several are clinically depressed going to bed hoping not to wake up. They have lost vision and everything that goes with that. Some have cataracts, as a result of their treatment as well as the disease itself, and cannot have surgery because their eyes are always inflamed. Those with the ability to self-fund do so. One family is funding adalimumab for their daughter while her brother receives the same drug from the NHSE for his Crohn's disease. Patients with idiopathic disease must have a second condition before they are considered 'exceptional.' Patients do not understand why blindness is not considered 'exceptional.' They do not understand why a therapy used successfully in rheumatology for over a decade is not available to them, yet an RA patient does not have to have a second condition in order to receive it.

Please list any concerns patients or carers have about the treatment(s) being appraised.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others? If so, please describe them and explain why.

Patients with idiopathic disease. Currently, if these patients fail combined immune suppressant therapy, there is no further medical therapy for them.

Those with diagnosed underlying disease may receive adalimumab for their systemic condition. Those with underlying disease controlled with first and second line therapies require funding to receive the dexamethasone implant. Agreement to fund is not uniform across the country.

Are there any groups of patients who might benefit less from the treatment(s) than others? If so, please describe them and explain why.

If intermediate uveitis is part of MS, adalimumab is contraindicated.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment(s)?

No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment(s) as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

If already available in the NHS, are there any side effects associated with treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

We are not aware of any.

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

consider such impacts.

Ophthalmologists will be aware of such patients. We think GP surgeries or outpatient rheumatology nurses could manage the adalimumab injections when adults are unable to do this themselves.

9. Other issues

Do you consider the treatment(s) being appraised to be innovative?

Yes If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

The dexamethasone implant provides an alternative to high dose oral steroid and its side effects. It is useful for patients who have no underlying disease requiring the use of immune suppressants. It seems to be effective when used together with a single immune suppressant and this is helpful for patients who need, but are unable to tolerate, a second immune suppressant. It may also mean that the dose of an immune suppressant could be a little lower which may mean a patient is more able to tolerate side effects. Problems with patient compliance are overcome.

Adalimumab is effective in severe, chronic disease reducing and preventing the flare ups in disease activity which ultimately lead to loss of vision. This is a step change in the treatment of sight threatening refractory uveitis, a step up in therapy which can change the lives of patients. Use of this therapy in uveitis could enable research into the optimum time to begin therapy with it to find out if earlier use would alter the course of the disease. The biologic therapy market is a competitive and expanding market and uveitis specialists are involved in the research connected with newer biologic therapies which will aid in the understanding of the complex processes which result in uveitis.

such If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

here any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Patients who fail combined immune suppressant therapy are losing their vision needlessly.
- Most patients want to be productive members of society who contribute to the economy rather than draw benefits from it.
- Uveitis patients should not be denied the therapies routinely available to rheumatology patients.
- Both therapies being appraised have demonstrated clinical effectiveness and are life changers.

- Uveitis research needs to be on a level with rheumatology research in order that the complexities of this disease are better understood and the suffering of patients reduced.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation statement (MTA)

Adalimumab and dexamethasone for treating non-infectious uveitis [ID763]

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment(s).

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to say which treatment (s) you are commenting on.

1. About you and your organisation

Your name: [redacted]
Name of your organisation: Royal National Institute of Blind People
Your position in the organisation: [redacted]

Brief description of the organisation:

RNIB is the UK's leading charity helping people with sight loss lead independent and fulfilling lives. An increasing focus of our work is on sight loss prevention and access to treatments. As part of this work we aim to ensure that patients are treated with new, clinically proven treatments as quickly as possible.

Our appraisal response has been informed through discussions with patients (including those on the VISUAL II trial and those treated with dexamethasone as private patients), clinicians and published research to:

- examine the impact of uveitis on quality of life
- explore current treatments
- assess the medications under consideration

As a result, RNIB calls on the NICE Appraisal Committee to recommend adalimumab (Humira) and dexamethasone (Ozurdex) for the treatment of non-infectious uveitis.

*Please note that this document has been completed in Arial 14, the RNIB standard for accessible documents, increasing the length beyond the recommended number of pages.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Uveitis is inflammation of the uveal tract of the eye, frequently impacting adjacent structures (vitreous, retina and optic nerve). Although infectious causes of uveitis are well recognised, in the

Western world most cases are non-infectious either relating to an underlying autoimmune/auto-inflammatory systemic disease or purely isolated to the eye(s).

Classified anatomically by the predominant location of the inflammation, posterior segment uveitis encompasses intermediate (middle section of the uveal tract, mainly vitreous humor) and posterior (the back of the eye, choroid, retina and optic nerve). Posterior segment uveitis is the most sight threatening form of the condition. There are three additional sight threatening complications of uveitis; these are cataract, glaucoma and macular oedema. Uveitis is defined as chronic when lasting longer than three months, or if relapse occurs less than three months after discontinuing treatment. Unlike many of the other main causes of sight loss, uveitis is common between 20 and 60 years of age.

What effect does uveitis have on vision?

Patients with the condition describe their sight as becoming blurry and distorted, ‘like looking through a greasy surface’ or ‘through mucky glasses’. Additionally patients report the loss of colour and depth perception. Developing uveitis and being made aware of the potential permanent loss of sight is naturally distressing to patients.

“I was 25 at the time, I didn’t want to go blind. I know how pretty everything can be. I had a fear that if I had children I wouldn’t be able to see them growing up”.

Patients living with uveitis experience a range of negative impacts common to sight loss as well as additional health problems resulting from current treatments (outlined in section four and five).

What is it like to live with uveitis?

Day to day life becomes challenging as patients have difficulty with basic activities from reading labels on food items when shopping, to reading text messages and newspapers, to cooking safely at home. Previously enjoyed leisure pursuits can become prohibitive and more complex and essential activities such as driving become problematic.

“I’ve done damage [to myself] when chopping things as I can’t see”

"You can legally drive with only one eye, but [if you have] two eyes working differently [it] causes, like a distorted vision and could at times feel very unsafe. I would have to shut the bad eye, [I] couldn't tell what was right and wrong."

This patient described the difficulties of simple driving maneuvers such as parking or driving away from a parking space. It was difficult for them to gauge what was 'right and wrong' in terms of their distance from other vehicles which could result in damage to them, their car and other road users.

Impact of uveitis on ability to work:

Loss of vision also has huge implications on working life as patients find they have difficulty performing tasks such as using a computer.

"[Uveitis had] a huge impact on my working life – I'm a sales rep and do lots of driving for work."

"That damage that was done is there, but if I can halt it I have my eyesight for life. If I did lose my sight, the social and economic implications…, I wouldn't be able to work and I would have to have care."

Individuals with uveitis may find themselves in difficult circumstances in relation their employment and economic stability if their employer or their work role has very little flexibility to take time off for medical treatment.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

The following treatment outcomes are important to uveitis patients:

- Restoring sight to the best possible degree
- Preventing further sight loss and blindness
- Reducing the impact of treatment on general health

Patients are realistic about the damage to sight caused by their eye condition (uveitis) and any secondary conditions. Primarily they want to preserve as much of their sight as possible and prevent further damage.

Patients also want to reduce the impact of the treatments on quality of life (e.g. serious side effects and the burden of subsequent frequent hospital visits).

Current treatments (steroids and immunosuppressants) can lead to additional health problems and decreased quality of life.

After a round of steroid treatment which led to increased eye pressure, one patient described “being in bits on the phone to my mum worrying about glaucoma”.

“The treatment was aggressive in my body, I put on weight, was awake in the middle of the night [because of the steroids]. The immuno drug I was very allergic to and it had an impact on my liver. I changed to another type and caught pneumonia and severe bronchitis. It was quite aggressive and made me very poorly.”

Patients find themselves on a cocktail of treatments to combat the related conditions as well as attending frequent hospital appointments. Dealing with uveitis alongside these additional problems results in huge disruption to normal life.

What is your organisation’s experience of currently available NHS care and of specific treatments for the condition? How acceptable are these different treatments and which are preferred and why?

Clinicians inform us that the standard treatment pathway consists of:

- First Line – steroid injections, systemic steroids
- Second line – Immunosuppressants
- Third line – biologics – anti-TNFs

The pros and cons of current treatments as perceived by patients and clinicians interviewed by RNIB are listed below.

Steroid injections:

Pros

- Steroid injections deliver treatment into the affected part of the eye as opposed to relying on drops to reach the location of inflammation.
- Steroid injections are local with and therefore limit the impact (of steroids) on the rest of the body
- Steroid injections are cheap in comparison to the new technologies examined in this appraisal

Cons

- Potential for temporary increase in intraocular pressure which if sustained may lead to secondary glaucoma. Glaucoma treatment compliance is known to be poor with risk of further sight loss or the need for surgery.
- Frequency of treatment leads to time away from work due to increased hospital appointments.
- Risk of faster developing cataracts (cataracts are common with all forms of uveitis). Cataract operations can only take place after three month remission. Chronic uveitis makes this difficult to achieve and prolongs stabilising steroid treatments. The trauma of cataract surgery could also induce further inflammation.
- Will not treat macular oedema, one of the related conditions of uveitis.
- Injections require regular administration by a clinician.
- Triamcinolone, a steroid used for injections is not licenced for the treatment of uveitis.

Steroid Implant (Fluocinolone)

Pros

- Longer lasting local steroid treatment as implant releases steroid over 2-3 years.
- Effective in some patients allowing them to cease additional systemic steroid tablets.

Cons

- In a significant number of patients fluocinolone implants led to increased intra ocular eye pressure resulting in glaucoma which comes with associated problems listed previously.
- High rate of cataract development with the use of the fluocinolone implant.

- No published research into the use of fluocinolone for uveitis, though it has been used to treat diabetic macular oedema.
- The current fluocinolone implant (Iluvien) is not biodegradable and remains in the eye. Patients will sometimes see the implant as a floater long after the treatment has been administered.

Systemic Steroids

Pros

- Treatment solution for bilateral uveitis.
- Treatment is very cheap in comparison to other treatments considered in this appraisal.
- Reduces inflammation.

Cons

- Side-effects on bone density, stomach, liver function, kidney function, mental health (including depression, agitation, mood swings), metabolic shifts and hair growth.
- Repeated flare-ups in chronic uveitis mean high doses have to be reinstated even after a patient has tapered their steroid treatment. Tapering may have to be given over a longer period to stabilise the condition and avoid flare-ups.
- Irritation of pre-existing conditions such as diabetes and high blood pressure.
- Immunosuppressants often have to be introduced alongside systemic steroids to assist in the tapering of steroid treatment. Immunosuppressants have many side effects detailed below.

Immunosuppressants (mycophenalate, mofetil, methotrexate, azathioprine)

Pros

- Stabilises uveitis in some cases.

Cons

- Serious potential side effects including impact on blood count, kidneys, liver and bone density.
- Regular blood tests required to maintain treatment.
- Risks during pregnancy.
- Mycophenalate is unsuitable for patients with rheumatoid arthritis
- Immunosuppressants are expensive.

- Off licence for the treatment of uveitis.

4. What do patients or carers consider to be the advantages of the treatment(s) being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment(s) being appraised.

Both treatments offer an alternative to exhausted treatment pathways that either have low efficacy or wide ranging negative impacts on general health.

Dexamethasone (Ozurdex) -

- Improved vision and restoration of sight to a 'reasonable level'
- Reduction of fluid in the eye and associated problems
- Side effects – patients consulted who were treated with dexamethasone reported that they experienced limited or no side effects.
- Increased quality of life – the local treatment removed the impact of steroids on the rest of the body, resulting in improved general health and reduced economic impact due to fewer hospital visits and the required time off work.

"I am living life normally with it."

Adalimumab (Humira) –

- Improved eyesight and reduced fluid in the eye (and associated problems).

- Easily self-administered treatment requiring only two fortnightly injections.
- Increased quality of life – the impact of systemic treatments on other parts of the body are eliminated resulting in fewer hospital appointments and additional treatments for secondary conditions.

“When I was offered the trial, I said that I can’t really afford to take more time off work to be part of a trial but actually it meant less time off work.” “They give me the medication to take at home.”

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England.

Dexamethasone (Ozurdex) –

- Improved vision in comparison to vision on current treatments.
- Increased quality of life in comparison to experience on current treatments.

“My quality of life is kept that way because I have the implant. I’d had enough of steroids; [they] would severely reduce my quality of life as I would be unwell. And I was unwell, very sick, getting plump, psychological effects, not mental illness but agitation and effects on my mood. I will not have steroids. I would have to let my sight go… I’m on high blood pressure control – it went haywire on [steroids]. I would be up then down and that happened three or four times over six weeks. The drugs that I need to take for diabetes were also affected and I didn’t need them, then I did, it was spasmodic on that treatment. [With Ozurdex] I avoid this, it’s local… three to four days and I’m back up…it works”.

“I’m living life normally with it”.”

“I had all the other injections, but steroid tablets – I wouldn’t consider at my age because of all the side effects that it would cause in your body and I’m only 49. The osteoporosis, liver failure, kidney failure - too big a risk… when one injection can do it. It’s more cost saving in the long run with all the extra visits and tests.”

Adalimumab (Humira) –

- Improved vision in comparison to vision on previous treatments

- Stability of condition in comparison to instability on current treatments.
- Reduction in side-effects compared to steroid and immunosuppressant treatments.
- Ability to live a normal life without the impact of side effects and frequent hospital visits.

“Adalimumab helped no end, I only have to go [to the hospital] every three months, I lost all the weight, I sleep better, I don’t bruise so easily, I don’t have time off work now as I’m very well, my uveitis is completely stable now. My eyesight is clear and has not got any worse.”

“The main thing is that it has stopped the main disease and its not impacting the rest of my body… It’s only treating the part of my body that needs treating, not taking too many pills, convenient treatment so it doesn’t impact on any other part of my life and stops my progressive eye disorder. And I don’t have to go to lots of hospital appointments.”

“My vision picked up tenfold, almost as good as before I was diagnosed. I’m still sensitive to light. If it wasn’t for the drug I would have given up… It took six months to start working but once that happened, it was the best decision I’ve ever taken.”

“Humira allowed me to appreciate my child after he was first born, to see his blue eyes.”

“It saved my vision so I’ll still be able to drive…gives me a lease of freedom that I didn’t have. [I] don’t have to have someone to go to the shops for me and read the labels…now I can pick flowers out on mum’s wallpaper and can read a text message in standard size. Before I had to zoom it in. Standard print is hard but before Humira even large print wouldn’t have worked. It’s a brilliant drug.”

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

None.

5. What do patients and/or carers consider to be the disadvantages of the treatment(s) being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Patients are clearly concerned by low efficacy of current treatments for uveitis and the resulting risks posed to their sight. Furthermore there is high concern over the damaging side effects of systemic steroids and immunosuppressant treatments currently offered.

Please list any concerns patients or carers have about the treatment(s) being appraised.

Dexamethasone (Ozurdex)

- Use of needles - there are some initial concerns and nerves about receiving an implant into the eye.
- Patients are willing to endure a short discomfort over the potential of losing sight.
- Financial implications and related stress - as dexamethasone cannot be universally accessed by NHS patients with uveitis (as it has not yet been approved by NICE); this can mean having to access it via private healthcare - a huge financial burden for individuals who feel that they can no longer tolerate systemic

steroids and/or immunosuppressants. Individuals are faced with a choice between loss of sight, severely reduced general health or major financial sacrifices. This is a stressful and precarious circumstance in which to live.

"It's ten minutes of fear vs. going blind or kidney failure. It's a no brainer."

Adalimumab (Humira) –

- Use of needles – patients mention the potential aversion to needles and associated fears around the requirement of self-administration
- Site rash following injections which reduces quickly – this was not a major concern.

"I can't see any disadvantages actually. Because I've had no side effects"

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

None

6. Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others? If so, please describe them and explain why.

Clinicians informed RNIB that Adalimumab may be more suitable for patients known to be vulnerable to steroid induced IOP (increase in eye pressure).

Both technologies being appraised offer an alternative to patients who may suffer from depression or other mental health problems that could be exacerbated by the use of systemic steroids.

Are there any groups of patients who might benefit less from the treatment(s) than others? If so, please describe them and

explain why.

Adalimumab is not recommended for patients who are pregnant or breastfeeding and it is suggested that patients wishing to conceive do not do so until five months after ceasing treatment. One patient responding well on the adalimumab trial had to cease treatment due to pregnancy and resume post pregnancy.

Adalimumab should not be used in patients with severe infectious conditions in the body including tuberculosis.

Dexamethasone implants are not recommended during pregnancy.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment(s)?

☐ Yes ☒ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment(s) as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

If already available in the NHS, are there any side effects associated with treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example,

qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Uveitis is common between the ages of 20 and 60 making those of working age groups are more susceptible.

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments? Please tell us what evidence you think would help

the Committee to identify and consider such impacts.

Adalimumab injections must be refrigerated, if a patient has working or other personal requirements that mean they are away from home on a regular basis this could be challenging.

9. Other issues

Do you consider the treatment(s) being appraised to be innovative?

☒ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

The introduction of a new class of drug in the second line of the uveitis treatment pathway is innovative. Anti-TNFs offer a step change in the treatment experience of patients who are un-responsive to steroid treatments whilst avoiding the serious side effects of immunosuppressants.

Are there any other issues that you would like the Appraisal Committee to consider?

We ask that the final guidance recognises the importance of rapid access to dexamethasone and adalimumab at the appropriate point in the treatment pathway, as the quicker a patient receives treatment the better their visual outcome is likely to be.

Although we are aware of the pathway suggested for dexamethasone and adalimumab, we are also aware that from speaking to patients receiving treatment via private practice that dexamethasone has been used early in the pathway to avoid the use of systemic steroids under the advice of the clinician. We therefore request that the guideline places dexamethasone as an option in the first line and as a preferable treatment to systemic steroids where only one eye requires treatment and where there are no additional conditions that require treatment via systemic steroids.

We are also request that Adalimumab (anti-TNF) is used in the second line alongside immunosuppressants (as per the licence) as opposed to being considered as third line to protect patients from the serious potential side effects of immunosuppressants.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Dexamethasone and adalimumab are effective and safe treatments stabilising non-infectious posterior segment uveitis and improving vision. Both treatments halt the damage caused to vision by uveitis.
- Dexamethasone and adalimumab offer additional choices in the treatment pathway. RNIB would like to see dexamethasone offered in the first line of treatment (to enable the clinician/patient to make an informed choice at the initial stage and have several options). RNIB would like to see adalimumab offered in the second line of treatment either alongside immunosuppressants or as an alternative to immunosuppressants.
- Uveitis patients being treated with dexamethasone and adalimumab experienced increased quality of life in comparison to treatment via current technologies. Patients report minimal or no side effects in comparison to the myriad of health complaints and additional treatments required when being treated with systemic steroids and immunosuppressants. This includes causing secondary eye conditions such as glaucoma.
- Patients treated with the technologies being appraised point to the reduction in economic impact on their own lives (e.g. a drop in the number of hospital visits and travel required as well as the impact on employment), but also the reduction in costs to the NHS and the public purse as additional treatments and care are no longer required.
- The Guidance for the use of dexamethasone and adalimumab should recognise the need for rapid access at the appropriate point in the treatment pathway, as the quicker a patient receives treatment the better the visual outcome is likely to be.

Appendix G – NHS organisation submission template (CCG and NHS England)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Adalimumab, dexamethasone and sirolimus for treating non-infectious uveitis

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Clinical Commissioning Groups (CCGs) and NHS England provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a CCG or NHS England perspective on the issues you think the committee needs to consider, are what we need.

About you

[redacted]

[redacted]

[redacted]

Name of your organisation: NHS England

Please indicate your position in the organisation: see above

- commissioning services for the CCG or NHS England specific to the condition for which NICE is considering this technology?

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

What is the expected place of the technology in current practice?

How the condition is currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Current NHS treatment for non-infectious intermediate, posterior and pan uveitis (and complicated anterior uveitis):*

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Short term: local corticosteroid injections (peri-ocular or intravitreal) or high dose systemic corticosteroid treatment (oral prednisolone or intravenous methylprednisolone)

Long term: low dose systemic corticosteroids and non-corticosteroid conventional systemic immunosuppressive medications

- Most commonly used: Mycophenolate mofetil and T-cell inhibitors (cyclosporine and tacrolimus)
- Sometimes used: Methotrexate and Azathioprine
- Rarely used: Cyclophosphamide and Chlorambucil

None of these drugs are licensed for the treatment of uveitis

Others:
- Anti-TNF alpha drugs are available for uveitis associated with JIA as part of several NICE TA's and adulimimab is available for paediatric patients under an interim NHS England commissioning policy for children with severe refractory uveitis (https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/11/d12x02-paediatric-uveitis-anti-tnf.pdf).
There is currently no access for adults except as part of the Individual Funding process.
- Dexamethasone intravitreal implants are also used widely in adults for the treatment of uveitis when systemic treatment is contraindicated, in uniocular disease and increasingly to induce short-term disease remission peri-operatively for cataract or glaucoma surgery (both glaucoma and cataract are complications of uveitis)

- Intravitreal methotrexate has been reported, but there is variable confidence among uveitis specialists in its efficacy and it is rarely used

*Complicated anterior uveitis is defined as intraocular inflammation limited to the anterior segment with secondary retinal cystoid macular oedema, raised intraocular pressure or cataract (all of which are sight threatening) or requiring 3 or more 6-8 week cycles of topical corticosteroid therapy per year

Is there significant geographical variation in current practice?

There is currently no routine access for adults to adalimumab and sirolimus. Some adults will have accessed treatment prior to the condition becoming the responsibility of specialised services and so there will be some variation in practice for existing products.
Are there differences in opinion between professionals as to what current practice should be?

There is absolute consensus among uveitis specialists with regard to the need for new treatments ; however some variation exists concerning the precise thresholds for

switching therapeutic category as well as exactly which drug to select in the context of each of the many sub-types of uveitis.

What are the current alternatives (if any) to the technology?

Alternatives to adalimumab:
- Other anti-TNF alpha drugs, eg infliximab and golimumab (etanercept can paradoxically induce uveitis and is not used)

Switching the type of anti-TNF alpha agent is a common strategy for optimising therapeutic efficacy (in particular between infliximab and adalimumab), and this parallels standard practice in other specialities (eg, rheumatology)

- Other biologics targeting:
    a.) other pro-inflammatory cytokines, such as interleukin (IL)-6 (eg, tocilizumab), IL-1 (eg, anakinra), and IL-12 / IL-23 (ustekinumab)
    b.) T-cell activation via CTLA-4 (eg, abatacept)
    c.) B-cells via CD20 (eg, rituximab)

In tertiary and quaternary uveitis clinics there are often plausible rationales on an individual case basis for the use of these agents (eg, ustekinumab in the context of sight-threatening uveitis associated with psoriasis or tocilizumab in juvenile idiopathic arthritis associated uveitis which has progressed to adulthood and is failing anti-TNF alpha therapy).

Alternatives to dexamethasone intravitreal implant and sirolimus intravitreal injection:
Fluocinolone acetonide is an alternative intraocular corticosteroid which is longer acting than dexamethasone and can also be administered in an intravitreal implant (Iluvien® – NB Retisert® is not marketed in the European Union). Iluvien® is not licenced for uveitis, but is occasionally used on an individual case basis via specialist uveitis centres as longer term local therapy when systemic treatment is contraindicated (or just one eye is involved).

[Sirolimus intravitreal injection: Following the European Medicines Agency's notification on 27 May 2016 that Santen has withdrawn its application for a marketing authorisation for Opsiria, we have not considered this technology in our responses.]

What are their respective advantages and disadvantages?

There is insufficient evidence to compare the newer potential options for uveitis. Decisions regarding their use are currently based on expert opinion, and are typically bespoke to an individual patient's clinical circumstances (NB there are multiple different sub-types of non-infectious uveitis).

To what extent and in which population(s) is the technology being used in your local health economy?

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Dexamethasone intravitreal implants are used widely according to the NICE TA and adalimumab is available for paediatric uveitis. For adult uveitis individual providers are using this treatment in patients judged most likely to benefit.

- is there variation in how it is being used in your local health economy?

Yes – There is variation with the use of anti-TNF where patients who accessed treatments under historical commissioning arrangements continue on treatment. There are examples where individual providers are providing treatment for patients whilst the policy for the use of adalimab for adult patients with severe refractory uveitis is being developed by NHS England in anticipation of the publication of the VISUAL II clinical trial.

NHS England is considering an interim policy for uveitis prior to the NICE MTA in adults but was awaiting the full publication of the aforementioned VISUAL II study now published, 18th August, 2016.

- is it always used within its licensed indications? If not, under what circumstances does this occur?

Yes. Adalimumab's prior use for uveitis in the NHS through exceptional funding routes falls within its newly licensed indication although at the time its use would have been off label.

The use of the dexamethasone intravitreal implant for uveitis in the NHS predominantly falls within its licensed indication; however it is also used in the context of complicated anterior uveitis, in particular for the control of secondary macular oedema and for the induction of disease remission prior to glaucoma or cataract surgery.

- what is the impact of the current use of the technology on resources?

Clinical operational resources are in place for the administration of adalimumab via existing specialist uveitis clinics (which are already initiating and monitoring patients' use of conventional systemic immunosuppressive treatments). The frequency of hospital visits and use of specialist service resources is decreased in patients who achieve drug-induced disease remission on adalimumab.

The drug cost to the NHS of adalimumab is currently £352.14 for one 40mg injection. This is administered alternate weekly. Therefore the cost of adalimumab for one year per patient is: 26 x £352.14 = £9,155.64 (adalimumab is VAT exempt because it is supplied by health care at home).

Dexamethasone intravitreal implants are already recommended by NICE for the treatment of retinal vein occlusions in the context of high-volume secondary care services. Hence the impact of using this technology for the orphan indication of non-infectious uveitis is similarly minimal.

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Adalimumab, dexamethasone and sirolimus for treating non-infectious uveitis

The drug cost for a dexamethasone implant (Ozurdex®) is £870 per implant plus VAT in addition to the procedure cost of £381 per day-case elective episode. The total cost for two implants per eye per year = £2850

- what is the outcome of any evaluations or audits of the use of the technology?

The analysis of a 10 year prospective audit of patients treated with anti-TNF alpha therapy for uveitis in an English regional service has been completed, but the results of this are not publically available.

We are unaware of any NHS audit or other evaluation data on the use of dexamethasone intravitreal implants for uveitis

- what is your opinion on the appropriate use of the technology?

Adalimumab
Patients with non-infectious intermediate, posterior or pan uveitis (or complicated anterior uveitis – see above) who are either:
1.) Refractory to treatment with more than 10mg/day of oral prednisolone and at least one conventional systemic immunosuppressive treatment.
2) Intolerant of conventional systemic immunosuppressive treatment, i.e. their overall general health is being put at risk of irreversible harm or treatment is otherwise contra-indicated.
3) At risk of rapid, permanent and profound vision loss, ie, severe immediately sight-threatening disease.

Dexamethasone intravitreal implant
Adult patients with non-infectious intermediate, posterior or pan uveitis (or complicated anterior uveitis – see above) who either:
1. Have a contraindication to conventional systemic immunosuppressive treatment
2. Require the induction of short-term local disease remission for ocular surgery (e.g., peri-operative for cataract extraction or glaucoma procedures)
3. Fulfill the above criteria for adalimumab treatment, but anti-TNF alpha therapy is contraindicated

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?

If NICE recommends these technologies the impact would be financial for NHS commissioners.

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The impact on patients would be purely in terms of the clinical benefit and wider health economic gain that NICE concludes will result from investment in these technologies.

As adalimumab and dexamethasone intravitreal implants are both already used widely in the NHS for other indications, the operational resources are already in place for their administration in this patient group.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?

Adalimumab should be administered through specialist (tertiary care) uveitis clinics using their existing resources and protocols for immunosuppressive drug counselling and safety monitoring.

The decision to treat patients with a dexamethasone intravitreal implant should similarly be coordinated by specialist uveitis clinics; however the implant can be administered in any secondary care ophthalmology service which already uses this technology in accordance with NICE recommendations for the treatment of retinal vein occlusions.

Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).

Adalimumab: see Appendix 2, pages 25-33 of the NHS England Clinical Commissioning Policy (July 2015) Infliximab (Remicade) and Adalimumab (Humira) as Anti-TNF Treatment Options for Adult Patients with Severe Refractory Uveitis (referenced in Appendix B for this Multiple Technology Appraisal – Final Scope)

The cost for the purchase of adalimumab itself for the orphan indication of non-infectious uveitis would be <1% of the total annual cost of anti-TNF alpha therapies to the NHS for other inflammatory diseases.

Dexamethasone intravitreal implant: see Cost Analysis, pages 8 and 9 of the North East Treatment Advisory Group (NETAG) 2012 Ozurdex® dexamethasone ocular implant for uveitis (also referenced in Appendix B for this Multiple Technology Appraisal – Final Scope)

Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?

These relatively high-cost technologies are already frequently used for other far more common indications in the NHS; hence the impact on the NHS budget as a whole will be relatively low in comparison.

However, in assessing resource implications it is also important to note that although non-infectious intermediate, posterior and pan uveitis (and complicated anterior uveitis) are managed in tertiary and quaternary specialist rare disease clinics, and therefore fall under NHS England's specialised services, current conventional systemic immunosuppressive drug costs (and the majority of dexamethasone intravitreal implants obtained through individual funding requests) are still paid for by CCGs.

Consequently, if NICE recommends the use of the technologies considered in this appraisal there will need to be an assessment of the distribution of this cost across NHS England's specialised services budget and CCGs. If NHS England bears the full cost this may impact the resources available for other specialised services.

Would there be any need for education and training of NHS staff?

There is a current wider national training need for NHS staff in the context of tertiary uveitis services (particularly with regard to specialist nurses, pharmacists and optometrists). This will not be affected by the commissioning of these technologies.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

No

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

No

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

No

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Not applicable

Other Issues

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Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology?

In the interests of equity of NHS investment in sight-saving medical innovations, it would be informative to undertake a health economic (cost-benefit) comparison between the technologies being considered in this appraisal and existing commissioned treatments for other pathologies involving the posterior segment of the eye (eg, age-related macular degeneration and vitreo-retinal surgery).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Adalimumab and dexamethasone for treating non-infectious uveitis

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Philip Ian Murray

Name of your organisation: International Uveitis Study Group (IUSG)

- (the IUSG is a select group of about 100 International Uveitis Experts)

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? Honorary Secretary
-
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

Not applicable

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Dexamethasone
The main indication for Dexamethasone is unilateral uveitic cystoid macular oedema – and the predominant type of uveitis associated with CMO is “posterior uveitis” (this is generally defined as inflammation affecting the posterior segment of the eye - posterior uveitis, panuveitis, intermediate uveitis). We are still unsure in which type of “posterior” uveitis the CMO has a better outcome. In patients who have an associated systemic disease that has also flared then systemic therapy may be more appropriate than just treating an eye. Otherwise patients with unilateral CMO and no associated systemic disease or if the systemic disease is well controlled then one would just treat the eye. This is standard practice. The initial treatment for unilateral disease is likely to be a periocular (sub-Tenon, orbital floor) injection of steroid e.g. triamcinolone. This may be effective in about 70% of patients but may last less than 3 months and can be associated with a significant rise in intraocular pressure. Failure of 1-2 injections would be an indication for a Dexamethasone implant as it lasts longer and is less likely to cause a rise in intraocular pressure. Evidence is from retinal vein occlusion studies, the HURON uveitis study and numerous case series in uveitis including looking at repeated injections. These studies have been summarised by Allergan and circulated to ophthalmologists as an aide memoire to assist in IFR applications. In patients with bilateral CMO we can give bilateral (usually sequential) periocular or intraocular injections but usually we resort to systemic therapy.

The Dexamethasone implant is widely used in all eye units for the treatment of retinal vein occlusion i.e. in secondary care. This would be undertaken in theatre or in a clean room.
There is a great variation in England in the ability to get funding for Dexamethasone. I believe there are 5 CCGs who have approved it. Otherwise the normal route would

be an IFR and there is little consistency between CCGs (some might approve and others might reject the application) and even in the same CCG (both myself and a colleague submitted an IFR to the same CCG for different uveitis patients – mine was approved but his was not). Recently, to my surprise, I have found Dexamethasone on the Blueteq system (online approval system for high cost drugs management) in my Trust. I do not know when it appeared or how long it will be there but it does allow me to obtain Dexamethasone for my patients as long as they have failed two other treatments.

Adalimumab

There are numerous published studies of varying levels of evidence to show that this drug has a major role in the treatment and prevention of sight threatening posterior uveitis. The indications would be patients with unilateral/bilateral sight threatening uveitis (this would also include patients with CMO) that has failed to respond or repeatedly recurs despite treatment with periocular/intraocular steroid, system steroid and a systemic immunosuppressant. At present the only treatment options we have would be to switch immunosuppressant or add in another immunosuppressant. There is no great evidence to show that doing this will be effective and another drawback is that each agent can take about 8 weeks to start working and one normally starts at a low dose that is increased as long as the blood monitoring tests are normal. Therefore the patients require a significant increase in prednisolone (with its well recognised side effects) during this 8-week period to treat the active disease by which time the immunosuppressant may or may not have taken effect. The initial recommendations (Clinical Commissioning Policy: Infliximab (Remicade) and Adalimumab (Humira) As Anti-TNF Treatment Options For Adult Patients with Severe Refractory Uveitis. Reference: NHS England D12/P/b. Prepared by NHS England Specialised Services Clinical Reference Group for Specialised Ophthalmology) suggested the Adalimumab would be indicated after a failure of 2 immunosuppressants, I personally feel this should be 1 for the reasons I have just stated. Although all drugs can have significant side effects if we needed to add in Cyclophosphamide then this could pose a major threat to fertility. As many of our patients are of child bearing potential then the main immunosuppressant we use, Mycopheolate Mofetil, could have devastating effects in pregnancy. At present it is felt that the ant-TNF drugs can be continued during most of pregnancy (http://www.behcets.org.uk/wp-content/uploads/2013/04/New-Pregnancy.pdf). We do not have any 3rd line agents so adalimumab cannot be compared to any other treatment.

NHSE has approved the use of Adalimumab for children with uveitis under the age of 18 years yet there are far more adults than children who require this treatment. The only way to try to get it for an adult is to do an IFR to NHSE but this is almost impossible to succeed because of the way they define exceptionality. This is a quote from James Palmer NHSE spokesperson from the minutes of a Specialised Services Stakeholder Surgery Meeting on 7th July 2015 in London on defining what NHSE mean by exceptionality “If there were no exceptional features anti-TNF treatment would therefore now not be funded. He illustrated this with the example of dental implants, where a patient who needed their teeth to write, as is sometimes the case for victims of the thalidomide tragedy, would be considered exceptional in comparison with other patients requesting dental implants.” The only ways anti-TNF

drugs can be obtained for uveitis patients is if they (a) have Behçet's Disease and attend one of the 3 National Centres of Excellence in England (Birmingham, Liverpool, London). The Commissioners have approved the funding for this, or (b) have another associated systemic disease, e.g. ankylosing spondylitis, psoriasis where funding for these drugs has been agreed for their systemic disease (also the type of uveitis normally associated with these conditions is anterior and not posterior uveitis).

Treatment is in the community and provided in pre-filled syringes via Healthcare at Home. I would expect this treatment to be only available to specialist uveitis centres. Regular blood monitoring is required and this is often undertaken through trained ophthalmology or rheumatology immunosuppression nurses

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The most important outcome measure and the most important sight threatening complication of non-infectious posterior uveitis is cystoid macular oedema (CMO). Clinical trials do not allow CMO to be used as a primary outcome measure/endpoint. The main measure that is used is vitreous haze. This is a scoring system that has had only rudimentary validation and involves assessing how clearly one can visualise the retina and optic nerve. Although vitreous haze will reduce vision it is purely the hazy vitreous jelly blocking the light reaching the retina. A 2-step improvement in vitreous haze is taken as a significant outcome. CMO results from inflammation

causing waterlogging of the retina at the most sensitive part – the macula. This causes structural change reducing central, reading and writing vision that may lead to permanent, irreversible damage to the macula. Also, it can be objectively measured using OCT. As CMO was not considered as a primary or secondary outcome in the recent Cochrane Systematic Review (Brady CJ, Villanti AC, Law HA, Rahimy E, Reddy R, Sieving PC, Garg SJ, Tang J. Corticosteroid implants for chronic non-infectious uveitis. Cochrane Database Syst Rev. 2016 Feb 12;2:CD010469) this makes analysis of trial data difficult. Anecdotally in my patients that have had a dexamethasone implant the CMO has resolved often with a dramatic return of vision. I have been pleasantly surprised at these good results. The side effects are well recognised – cataract, raised intraocular pressure but it is the only intravitreal steroid that has the best side-effect profile and less likely to cause these problems than other preparations.

Although both technologies can be used to treat CMO, in clinical practice it is the main indication for dexamethasone.

There are many studies on adalimumab that have been mentioned in (Clinical Commissioning Policy: Infliximab (Remicade) and Adalimumab (Humira) As Anti-TNF Treatment Options For Adult Patients with Severe Refractory Uveitis. Reference: NHS England D12/P/b. Prepared by NHS England Specialised Services Clinical Reference Group for Specialised Ophthalmology).

There are at least 2 publications on quality of life and the HURON dexamethasone study (it is relatively unusual for commercial trials to report their quality of life results):
Naik RK, Rentz AM, Foster CS, Lightman S, Belfort R Jr, Lowder C, Whitcup SM, Kowalski JW, Revicki DA.
Normative comparison of patient-reported outcomes in patients with noninfectious uveitis.
JAMA Ophthalmol. 2013 Feb;131(2):219-25.

Lightman S, Belfort R Jr, Naik RK, Lowder C, Foster CS, Rentz AM, Cui H, Whitcup SM, Kowalski JW, Revicki DA.
Vision-related functioning outcomes of dexamethasone intravitreal implant in noninfectious intermediate or posterior uveitis.
Invest Ophthalmol Vis Sci. 2013 Jul 18;54(7):4864-70.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

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- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

It is essential to get the views of all stakeholders including patients, carers, patient advocates and patient groups. I am satisfied that they all have had the opportunity to comment and have not been excluded. I do not think are any equality or diversity issues.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

As far as I am aware there is sufficient published information for Dexamethasone and Adalimumab although a number of papers are case series,

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Dexamethasone Intravitreal Implant
This is given routinely for retinal vein occlusion and facilities are readily available i.e, clean room/theatre in all eye units. Nursing staff already appropriately educated.

Adalimumab

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Multiple Technology Appraisal (MTA)

This is arranged through Healthcare at Home. I would expect this treatment to be only available to specialist uveitis centres. Regular blood monitoring is required and this is often undertaken through trained ophthalmology or rheumatology immunosuppression nurses.

Adalimumab and dexamethasone for treating non-infectious uveitis

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you
Your name:

Srilakshmi Sharma

Name of your organisation

OxFord Eye Hospital, John Radcliffe Hospital , Oxford, OX3 9NE

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- Yes

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

Yes

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?

Yes

I am a member of staff and lead for Clinical Governance

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

[]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

This condition is currently treated with one or more immunosuppressant agents and doses of steroids (standard therapy) which may exceed recommended guidelines (over 10mg/day long term). The disadvantages are that 40% fail to respond to one or more immunosuppressant agents and low dose prednisolone (steroid) .

Prednisolone in a dose above 7.5mg/day given long term causes multiple morbidities including stroke and heart attack. Physicians resort to using this drug in large doses in an effort to save sight once they have exhausted the options with standard therapy.

Professionals are all of the opinion that Adalimumab represents a very effective therapy in generating sustained remission when patients are unable to tolerate standard therapy or when current therapy is ineffective. As a group, clinicians are less clear on whether it should be given as the very first drug in a patient presenting with severe uveitis. There are no current suitable alternatives in terms of escalation of therapy for those patients failing to respond to standard care.

There is no variation in practice across England as NHSE are the gatekeepers and barely anyone gets treatment despite extensive effort placed into attempting to generate a policy document. IN Scotland, there is an acceptance of the role of anti TNF agents in uveitis and guidelines which direct treatment

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

It is not known whether certain subgroups respond more or less. There is insufficient power in any one study to distinguish the rate of response between all the diseases which cause uveitis. Currently all groups appear to demonstrate response. However, it should be contraindicated in individuals with demyelination

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

The product should be used in secondary /tertiary specialist uveitis centres with a dedicated uveitis specialist nurse with ability to participate in counselling and immunosuppression monitoring. The consultant should be trained in Uveitis as a subspecialty. Adequate pharmacy support should also be available to audit drug use monitoring in hospitals and arrange distribution of drug eg delivery to the home as GPs canot prescribe.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Adults: The product has only just been licensed. The technology is available but rationed by NHS England through the IFR program. In essence, the IFR pathway does not permit the vast majority of patients to obtain therapy unless there is exeptionality. Because uveitis is no longer exceptional , even deserving cases do not get funding for antiTNF therapy. Thus, patients are losing sight needlessly

Children: NHS England have issued a policy which enables children with uveitis to be treated with adalimulab. The guidelines are set out in NHSE interim commissioning policy for paediatric uveitis on the basis of overwhelmingly positive evidence for juvenile idiopathic uveitis following the SYCAMORE trial in the UK .

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

1. Levy Clarke G et al: Expert panel recommendations for the use of antitumour necrosis factor biologic agents in patients with ocular inflammatory disorders, Ophthalmology 2014

2. Scottish Uveitis Network guidelines for anti tumour necrosis factor treatments www.Sun.scot.nhs.uk.

The methodology used was appropriate. In, 1. a robust systematic review of Class I and II evidence was performed to synthesise the guidelines amongst international uveitis experts.

In 2, a consensus panel reviewed all available literature and all competing technologies to design guidelines appropriate for Scotland. These are currently in practice.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

This technology has to be delivered by subcutaneous route. However, this is only once every two weeks and many patients use methotrexate subcutaneously also. The drug can be delivered home by certain distributors so this is not an issue. Patients have to be taught how to administer the drug and also whom to notify if they develop either side effects or infections. There are currently no additional mandatory tests.

However, if patients stop responding to the drug, it is sometimes useful to send for adalimumab antibodies to determine if this is the cause. In general, to avoid this scenario, adalimumab is usually given with another immunosuppressant.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or

to assess response and the potential for discontinuation.

Starting therapy is dependent on failing existing modalities of treatment. This is an acceptable strategy for which there are no formal timelines and is based upon a clinical assessment of response to drug
Patients cease therapy when patients disease activity increases or fails to be controlled on therapy. This is a clinical judgement with no formal guidelines.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The clinical trial represents the decisions made in clinical practice in terms of the outcomes which are very realistic as a whole. In reality, patients have poor vision at less vitreous haze than that specified in the trial. This inclusion criterion is one which the FDA imposed rather than one selected by clinicians who would find 1+ vitreous haze an acceptable inclusion criterion.

30% of patients lose vision due to cystoid macular oedema (CMO). This is a consequence of active uveitis rather than a primary activity indicator. However, the presence of CMO would be a criterion for treatment with adalimumab in the clinic. In the trial, CMO was not an inclusion critierion although its presence at 1 year in placebo and adalimumab-treated patients was assessed and showed a 55% improvement. If we do not have CMO as an inclusion, it will result in undertreatment of patients.

One of the endpoints for treatment failure was anterior uveitis. In reality, most patients would be treated with an increase in topical steroids before stopping biologic therapy. This results in undertreatment of patients.

The applicability of VISUAL trial results to patients in the UK may be limited as the standard of care is treatment of uveitis with at least one immunosuppressive agent and secondly, the current treatment goal is steroid withdrawal to low dose rather than cessation. However, a pragmatic approach may be taken whereby, adalimumab can be used as add-on therapy in the UK setting.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

All side effects are predictable and we now have several years of data from rheumatoid arthritis and ankylosing spondylitis also to assist us in evaluating adverse

events. These data are consistent with the VISUAL studies and tell us that adalimumab is well-tolerated by patients and quality of life is improved significantly with Adalimumab despite any adverse event profile. In general, the incidence of infections is the biggest problem but reduction to 5mg/day or cessation or steroids will reduce this risk four fold at least in rheumatoid arthritis data. We cannot assess this for uveitis patients yet as we lack phase IV data.

Equality and Diversity

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- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

No to all questions above.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Registry data from the UK (to be published late 2016) are found on page 9 of NHSE policy consultation document
https://www.engage.england.nhs.uk/consultation/specialised-services-consultation/user_uploads/uveitis-adults-policy.pdf

Key data are as follows

All patients (n=41) on biologics showed clinical remission after a mean (± SD) follow-up of 1.36(± 0.88) person years.

•

Higher proportion of patients (48.78%) showed improvement in visual acuity as compared to patients (17.07%) showing worsening in visual acuity after a mean (± SD) follow-up of
2.51(± 2.01) and 4.38 (± 3.50) person years, respectively

•

88.89% of patients on biologics showed reduction in steroid dose to ≤10 mg, followed by 75.85% of patients showing reduction in steroid dose to ≤5 mg, and 45.16% completely stopping Prednisolone use after a mean (± SD)
follow-up of 3.06 (± 2.32), 3.15 (± 1.76), and 3.49 (± 1.59) person years, respectively.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Where uveitis centres lack a nurse involved in monitoring or counselling, funding to ensure a proportion of nursing time is dedicated to counselling, training patients and monitoring immunosuppression monitoring. Much training may be provided by rheumatology departments who use this drug in large quantity. Additional pharmacy support include methods for delivering drug to patients so they do not have to visit the hospital to pick up medication. Again, rheumatology departments will have set up the infrastructure within hospitals.

http://www.moorfields.nhs.uk/T&Cs

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Patient/carer expert statement (MTA)

Adalimumab and dexamethasone for treating non-infectious uveitis [ID763]

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment(s).

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to specify which treatment (s) you are commenting on.

1. About you

Your name: Alison Mapstone
Name of your nominating organisation: Birdshot Uveitis Society
Do you know if your nominating organisation has submitted a statement?

☑ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☑ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☑ Yes ☐ No

- a carer of a patient with the condition?

☐ Yes ☑ No

- a patient organisation employee or volunteer?

☐ Yes ☑ No

Do you have experience of the treatment(s) being appraised (that is, those included in the title)?

☑ Yes ☐ No

If yes, please tell us which one(s)

Adalimumab injection, also called Humira.

If you wrote the submission from the patient organisation and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

My timeline is as follows.

My visual disturbances started back in 2010 with 'flashes and floaters'.

Visual disturbances escalated to the point of seeing clinicians on two occasions in late 2011 – at this time being told these types of visual disturbance are common in women of my age. Situation worsening (vision appeared to be wobbling, oscillating,

vision clouded with what can only be described as spatter effect, as if a toothbrush with black paint has been 'flicked' all over useable vision, big floaters, and the Vaseline effect – where it appears that someone has smeared Vaseline all over your glasses and you try to look through them – only you haven't got your glasses on at the time). A friend told me to go to an optician with an OCT scanner in August 2012, who made an immediate referral to Ophthalmology at my local hospital where they took the condition and my symptoms seriously (at this point visual acuity in right eye was 6/36 due to oedema). After various tests, a consultant, who thankfully was aware of my condition, did a specialised blood test and discovered I had Birdshot Uveitis (birdshot chorioretinopathy) and that it was in a large state of flare-up.

From September 2012 I was monitored and given steroid eye drops and an orbital injection of steroid to try and calm the situation initially. A month later, I was prescribed oral steroids (starting at 60mg prednisolone daily) and mycophenolate mofetil to try to suppress the immune system, as the inflammation was still not reduced. This regime was barely stabilizing the condition, and on trying to reduce the steroids in March 2013 a flare-up occurred, so in addition to the mycophenolate I began taking tacrolimus as a third-line immunosuppressive therapy to see if it would contain the problem and allow me to reduce the steroid. I had to stop taking the tacrolimus after one month because of extreme side effects.

I was so fortunate in November 2013 to begin treatment with Humira in addition to the oral steroids and mycophenolate. Visual acuity is now 6/6 to left eye and 6/7.5 to right, eye pressures well controlled, with no sign of macular oedema or active inflammation. The other medications (prednisolone and mycophenolate) are very slowly being tapered down.

That's the 'science bit', but living with the condition, especially before Humira, well, for me, the overriding feelings were helplessness and fear. When my vision started to deteriorate, I would get frustrated, trying to rub my eyes to make them see better. Staring at anything in detail became useless, blurry – a clear blue sky didn't exist any more, it was foggy, black splatter, distorted. I remember walking in a wood near my home in autumn, and because there was a lot of dappled shade I could get at least a feeling of what the wood used to look like, if not in detail. Bright sun, even with sunglasses, was painful (a good 6/10) as if you wanted to turn your head away, and driving, in even twilight, let alone dark, with oncoming headlights and street lights was a no-no – that was a 10/10! (Actually, given my acuities at the time, I probably shouldn't have been driving at all, but daily life needs to go on and I was desperately trying to keep normality going). I am a therapist for a living: aromatherapy, massage, reflexology, herbalist, etc, and fortunately I am self-employed. My clients were amazing, and because I knew them all so well, they didn't seem to mind a squinting therapist. I found early on that if I closed my eyes I could 'see' their bodies via touch and still treat them – but I stopped advertising and would only take close referrals from friends who knew about my condition. New situations began to be a challenge: navigation around the home is one thing, and possibly the local area, but being about an inch from a can of beans to read ingredients in the shop, groping for change, looking at a book, computer screen, etc, it simply got to the point where I couldn't be bothered - it was too tiring and truly depressing. My husband is a brick. He changed the lighting in the house so I wouldn't get glare, especially in the kitchen where I needed good light to see what I was doing (but not the acid bright of normal light to make me squint). He changed taps so I could use them without having to grip (as I developed joint pains from a medication side-effect), found a wall-mounted

magnifying mirror to try and enable me to still do the little things, like pluck my eyebrows, tried to do everything he could to help this scared, grumpy, depressed woman to try and keep hold of everyday life. I didn't really want, or couldn't be bothered, to leave the house much any more - it was easier to stay in familiar surroundings, and my world began to shrink. I started to lose the joy of anything and everything really, oh, and then there's the medication.

Picture if you will a paper bag almost the size that Ryanair would class as non carry-on luggage, full to the brim with steroids, immune suppressants, tablets to keep your bones strong, ones to prevent stomach ulcers – a large white board was required to timetable a medication regime executed with military precision. Because of the large amount of steroids required to control inflammation (60mg daily), insomnia resulted: no sleep for weeks at a time, just rest when you can, but I was so wired, it was a slippery slope down. I was offered sleeping tablets but the side-effects scared me and I didn't take them. My face swelled up, I became aggressive, moody, grumpy, tearful, and oh yes, well and truly paranoid. The medications triggered early menopause symptoms. I was getting more and more depressed, and my condition was not stabilizing. Tacrolimus was prescribed. After a month or so, at what was described later as practically a non-therapeutic dose, about a third of my hair fell out, I became jittery, shaky, suffered palpitations and sky-high blood pressure resulting in a dawn visit to A&E, and a quick withdrawal of tacrolimus. With the situation becoming dire, miracles are now required (I am at this point even trying to train my own dog to help me just in case the lights go out completely) - and my consultant managed to acquire Humira for me. November 2013: the first step back to normality.

The impact of Humira on my life has been little short of miraculous. It may sound corny, but it has quite literally given me back my life.

After just a couple of months, my vision started to clear: I could see detail much easier. Because the Humira is working so well for me, my medications are slowly but surely being reduced. My mood swings, depression, paranoia, joint pains and tiredness are but a ghost of their former selves. I run workshops now on herbalism and complementary therapies, my client base has swelled, I drove a 120-mile round trip the other week to visit relatives, I can see to do the dusting (well, I can now if I choose to, but there's always so much more fun stuff to do), I can do the gardening - the list goes on. And every day, each and every day, there are always so many wonderful things to see – a drop of dew on a flower or leaf (if you look closely you can sometimes see your own funny reflection!), your friend's face, your own face, even that can of beans from a distance – and I am so very grateful for having the opportunity to have Humira.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

Treatment on Humira has enabled me to see again. I would like the treatment to continue being effective for me and enable me to remain stable with the minimum of other medications. This would be beneficial, as less medications means less compound side-effects and long-term toxicity. Having one fortnightly injection is convenient and allows me to simply get on with a near to normal life.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

My GP and consultants are a truly amazing group. I feel supported, listened to and cared for by them. Clinics are thorough and times between seeing my consultant are regular. I am aware of the huge pressure the consultants are under to see everyone, and I am very grateful that I do get to see my chosen consultant each time to help me with continuity. I do think ahead and normally call the booking office in plenty of time to get an appointment as close to my three-month recalls as possible. As long as I am proactive, it all seems to work well.

Regarding specific treatments, I realise the first line is normally steroids and mycophenolate. Due to the high doses of steroid normally required to stabilize, I found the side-effects really unpleasant, affecting not only myself but impacting on my lifestyle, mental health, family, friends and work. The mycophenolate is slightly more tolerable, but always being aware that I have to keep up with regular blood tests, good hydration and a good diet, etc, because of toxicity issues, and always the concern of long-term use effects. The next line of defence such as tacrolimus for me was as described above: completely unacceptable due to my utter intolerance of it.

4. What do you consider to be the advantages of the treatment(s) being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment(s) being appraised.

My condition has been stabilized by Humira. I have no visual concerns. My eye pressures are well controlled with excellent visual acuities of 6/6 and 6/7.5. No signs of active inflammation and no macular oedema. Being on Humira appears to

present only the negligible side effect of sporadic sinusitis; and a slightly woozy feeling after initially injecting (which disappears if I eat chocolate). Since starting Humira, my joint pain has also decreased, other medication has also been reduced, and because my eyesight is 'normal' for want of a better word, I can do everything I used to be able to do. Thus, my quality of life has improved dramatically. My business is back on track and improving all the time, I can travel, meet with friends, go shopping: everything that people normally take for granted that was slipping so quickly from my grasp, is back. My husband doesn't need to be running around trying to do everything for me any more, we're back on an equal footing, and I am certainly a far more stable person mentally than before I was on Humira. Humira is very easy to use: I can inject it in the comfort of my own home, once a fortnight, and then get on with my life.

Please explain any advantages for the treatment(s) being appraised compared with other NHS treatments in England.

I think the Humira treatment has advantages over other NHS treatments in England. The medication only has to be taken fortnightly; it appears to have very few side effects for me (although I have taken it for only a couple of years). Personally, I found it extremely quick and effective in stabilizing and controlling my condition. It is far easier to take the one injection once a fortnight, as opposed to a daily box full of tablets, all at different times, etc.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

5. What do you consider to be the disadvantages of the treatment(s) being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Generally, the side effects and long term use of the current treatments concern me. Steroid side effects are especially unpleasant. Although I appreciate all long-term medications can have downsides, toxicity can be a real issue. Mental health can suffer considerably. Conditions can be slow to respond to the treatments.

Please list any concerns you have about the treatment(s) being appraised.

Principally, long term safety (toxicity). Also, Humira has to be kept refrigerated, so this can have an impact on travelling, holidays, etc, trying to work round 'injection day', or transporting medication in such circumstances. Power cuts.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

6. Patient population

Do you think some patients might benefit more from the treatment(s) than others? If so, please describe them and explain why.

As long as the patient can tolerate the Humira, I can only see benefit from them taking it. It could result in more successful outcomes of treating and stabilizing their conditions (quicker), and reducing other medications currently being used (and side effects felt), thus placing less strain on NHS providers and medications costs.

Do you think some patients might benefit less from the treatment(s) than others? If so, please describe them and explain why.

I think some patients might benefit less only if they could not tolerate the Humira. The injection is a needle, so if they were needle phobic, that may not help, but it is in pen form, so you hardly even see it go into the body, and it's very easy to use.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment(s)?

☐ Yes ☑ No If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment(s) as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

If already available in the NHS, are there any side effects associated with the treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

9. Other issues

Do you consider the treatment to be innovative?

☑ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

This is only my personal view and experience. Humira has reduced my symptoms and controlled my condition when the normally accepted medications have not. I have found my body appears to tolerate the Humira well, and the convenience and ease of once a fortnight injection is great. I have noted that unpleasant side-effects of the original medications have considerably lessened as their amount has been reduced, and the new side effect of Humira (only really sporadic sinusitis) is so small it's hardly worth mentioning.

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- **Life-changing** – empowering. Giving me my life back. It has had a profound effect on my life.
- **Cost-effective** – self-worth; valued member of society; not a burden; I can work.
- **Hope** – more successful treatments; fewer compound side effects.
- **Availability** - access to all who could benefit.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (MTA)

Adalimumab, dexamethasone and sirolimus for treating non-infectious uveitis

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment(s).

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to say which treatment (s) you are commenting on.

1. About you and your organisation

Your name: Maxine McCarthy

Name of your organisation: Olivia's Vision

Your position in the organisation: 'Expert Patient'

Brief description of the organisation: Please see OV response.

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None.

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Living with the condition

Living with idiopathic, chronic bi-lateral pan uveitis is easy for me these days. Anti-TNF therapy (infliximab) has placed my condition into drug induced remission, I have a visual acuity of 6/6 in one eye and 6/12 in the other. The better eye has a pale optic nerve as a consequence of corticosteroid but this has not resulted in loss of visual field, while the weaker eye has reduced colour vision and provides distorted sight from early cystoid macular oedema which persisted, despite all therapies employed. A methotrexate injection into the eye may resolve this long standing oedema but at this late stage, if successful, it is unlikely that any of the vision lost so early in my disease could be recovered. I think my case makes clear how important it is for uveitis specialists to have access to funding for therapies, like the dexamethasone implant and adalimumab, before their patient loses vision irreversibly.

My life today has purpose and contains pleasure. I enjoy a good quality of life. Although I had to retire early because my vision was so unreliable, I found employment in a related field which supplements my pension and enables me to contribute to society. Being able to work is very important to me. Anti-TNF therapy gave me back the life I enjoyed before uveitis and I am immensely grateful to receive it. To be sighted again far outweighs the inconvenience of travelling thirty miles to receive treatment and the fact that, today, I drive those thirty miles absolutely delights me.

Living with pan uveitis before anti-TNF therapy commenced was very difficult. My disease was stubborn and aggressive. I was already blind in my presenting eye three months after diagnosis when I transferred to specialist care. While the other eye still had good vision, I lived with the knowledge of how quickly uveitis can take away sight. A year after diagnosis, retinal vein occlusion had occurred in both eyes, the presenting eye had had inflammation of the optic nerve, the better eye had problems with steroid induced high ocular pressure and both eyes had the beginnings of cataract. Despite corticosteroid injected into the thigh to help both eyes and three infusions of steroid over the course of a week, the macular oedema in the presenting eye remained and vision in the other eye dropped. There was no escaping the presence of uveitis; when vision was marred by many floaters and much debris swirling around inside my eyes, even the most beautiful sunset became ugly.

Vitrectomy had been planned for my presenting eye after the failure of the initial corticosteroid. Despite beginning therapy with methotrexate and adding ciclosporin, the intraocular inflammation continued and vitrectomy was out of the question. Two years after diagnosis, my vision was ‘hand waving.’ There was now little to lose and treatment was changed to cyclophosphamide in the expectation that this would quell inflammation and provide a window for surgery. For the first time, after several infusions of cyclophosphamide, the inflammation stopped and both eyes received combined vitrectomy and cataract surgery with injections of avastin. This complex surgery was successful and all who examine my eyes marvel at the skill of the surgeon. I

leave it to the uveitis professionals to debate the point at which beginning anti-TNF may have made a difference to the course my disease took. Being a steroid responder, and suffering horribly from the side effects of various glaucoma medications, I'm not sure I would have been happy were dexamethasone implants to have been used, although an implant may have spared me the side effects of the steroid pulses I received.

Some months after surgery, having restarted methotrexate and ciclosporin, inflammation recurred and cystoid macular oedema was back in the better seeing eye. Private health insurance funded courses of Lucentis for both eyes and I would have good sight restored within hours of receiving the injections. However, anti-vegf is not a long term solution for uveitis and I'm not sure what would have happened next if my PCT had not agreed I was an exceptional case and funded anti-TNF. I will never forget the day of the loading dose. Central vision started to return on the ward an hour into the infusion, and three hours later, I knew my combined visual acuity was 6/6 near enough.

How did I feel as all this occurred? With the compassion and kindness of my uveitis specialist and rheumatologist, I endured it is the simple answer. When sight is lost, one's whole life changes dramatically: income reduces, independence is lost, some of the pleasures of life, like reading, (talking books are not the same!) are impossible. What makes uveitis particularly difficult is that others don't understand it so emotional support may be lacking and few fully sighted people have any idea of the world in the way uveitis patients see it. I found other uveitis patients online and they helped me through the worst. Having these other patients as new friends meant I could stop talking to others close to me about the disease and this helped remove strain from some relationships. When vision was impaired, I learned to do things differently and I discovered when I was out and about that strangers were only too happy to help. One stranger helped me post a letter when I couldn't find the slot in a post box. My large garden looked the best it was ever to look when green fingered friends took it on as a project. By the time sight was restored, I had a screenplay written on my computer in huge .38 text. One

finds ways to occupy the mind and distract from misery but there are still numerous duvet days.

2. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

The outcome important to me is good visual acuity. This gives me quality of life, enabling me to drive and to read. When I was receiving cyclophosphamide, the outcome I wanted was the cessation of inflammatory activity so that cataract surgery and vitrectomy became safer. With glaucoma drops, my preferred outcome was more focused on tolerable side effects than percentage reduction in ocular pressure. Blepharitis I can accept, depression and cystoid macular oedema, I cannot.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these different treatments and which are preferred and why?

With the early loss of vision in my disease, I had difficulty accepting that initial therapy is corticosteroid which causes cataract and places patients at risk of high ocular pressure. High dose corticosteroid infusions were something I refused to repeat. Life was not worth living and I was impossible to live with.

Of the immune suppressants, methotrexate has been the easiest for me. It's taken weekly as opposed to ciclosporin and mycophenolate mofetil which are taken daily, and it does not require me to take it at specific times in relation to eating. While I may experience mild nausea if I take it on waking, I sleep through this when taken before bed. I have thick hair so I am not troubled by the thinning of hair. Being rather fond of red wine and gin, I felt very hard done by when my rheumatologist banned both. After six months of good liver function tests, one bottle of red wine a week was allowed and I was told which day to take my methotrexate and which days, note the plural there, this wine

could be enjoyed. I drink fine red wine now and methotrexate prevented uveitis tipping me into alcoholism as a coping strategy. I developed an allergic skin rash when the hospital changed the generic and had the inactive ingredient responsible not been identified, I would have had to change this immune suppressant to mycophenolate mofeitil. My methotrexate, sans silica, is now supplied by a local pharmacist.

Ciclosporin was relatively easy to take twice daily although I disliked the smell of the large capsules. Side effects were somewhat unpleasant and troublesome. I found the natural cycle of my days changed from 24 hours to 26 hours and if I ever managed to stay asleep for six and a half hours, that was a good night's sleep. There were occasional, brief twinges of leg muscles. Had the drug stopped inflammation, I would have tolerated the side effects.

Cyclophosphamide was accepted and the side effects clearly explained, along with measures to reduce the risk of cancer of the bladder some years after the drug was used. I was blind, I wanted surgery, there was no choice about having these infusions. Had I been a younger woman who wished to have children, I don't know whether I would have accepted the risk to fertility.

Tacrolimus was a nuisance in that it couldn't be taken with food. The dose I took was rather high and I only managed ten days of treatment before I found myself spending the day on the sofa staring blankly into space. It made no difference to inflammation.

Infliximab has been the best treatment of all for me. It works very quickly, it resolved, and then kept away, cystoid macular oedema in one eye. The only downside is that I am extra careful about avoiding infection. I have had to have infusions delayed when I have a cold sore or I catch a cold and since eight weekly infusions meant my sight was blurring between infusions, I become anxious about delays. This therapy has been such a life changer for me that it upsets me to know new patients are currently denied it.

3. What do patients or carers consider to be the advantages of the treatment(s) being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment(s) being appraised.

Responses to the remaining questions are given as Olivia's Vision responses.

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

4. What do patients and/or carers consider to be the disadvantages of the treatment(s) being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)

- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Please list any concerns patients or carers have about the treatment(s) being appraised.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

5. Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others? If so, please describe them and explain why.

Are there any groups of patients who might benefit less from the treatment(s) than others? If so, please describe them and explain why.

6. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment(s)?

No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment(s) as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

If already available in the NHS, are there any side effects associated with treatment(s) being appraised that were not apparent in the clinical trials

but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

7. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Other issues

Do you consider the treatment(s) being appraised to be innovative?

☐Yes. Yes

Are there any other issues that you would like the Appraisal Committee

to consider?

8. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

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-
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Adalimumab and dexamethasone for treating non-infectious uveitis

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Clinical Commissioning Groups (CCGs) provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a CCG perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name: **Nicola Symes**

Name of your organisation **NHS England**

Please indicate your position in the organisation:

- commissioning services for the CCG in general?
- commissioning services for the CCG specific to the condition for which NICE is considering this technology?
- responsible for quality of service delivery in the CCG (e.g. medical director, public health director, director of nursing)?
- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. participation in clinical trials for the technology)?
- other (please specify) **Lead Commissioner for Specialised ENT and Ophthalmology Clinical Reference Group (CRG), Specialised Commissioning, NHS England.**

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NIL

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

As per NHS England organisational response

To what extent and in which population(s) is the technology being used in your local health economy?

- is there variation in how it is being used in your local health economy?
- is it always used within its licensed indications? If not, under what circumstances does this occur?
- what is the impact of the current use of the technology on resources?
- what is the outcome of any evaluations or audits of the use of the technology?
- what is your opinion on the appropriate use of the technology?

As per NHS England organisational response

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?

As per NHS England organisational response

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?

As per NHS England organisational response

Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).

As per NHS England organisational response

Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?

As per NHS England organisational response

Would there be any need for education and training of NHS staff?

As per NHS England organisational response

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

As per NHS England organisational response

Other Issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology.

As per NHS England organisational response