Gevokizumab for chronic non-infectious uveitis

SUMMARY

Gevokizumab is an anti-inflammatory humanised IgG2 monoclonal antibody that binds to interleukin-1β (IL-1β). It is intended for treatment of chronic, non-infectious uveitis, including that associated with Behçet’s disease. Binding to IL-1β blocks the activation of the IL-1 receptor preventing cellular signalling events that produce inflammation. Gevokizumab is intended for monthly subcutaneous (SC) dosing.

Uveitis is inflammation of the uveal tract of the eye, which consists of the iris, the ciliary body and the choroid. Inflammation of nearby tissues, such as the retina, the optic nerve, and the vitreous humour may also occur. Uveitis may be classified by the anatomical location of the pathology: anterior, intermediate (vitrilis), posterior (retina and choroid) or panuveitis. Chronic uveitis may be defined as active uveitis that persists longer than three months. Symptoms of uveitis include: pain, redness, photophobia, headaches, visual floaters and decreased visual acuity. Non-infectious uveitis may be due to an underlying inflammatory condition, an autoimmune disorder or occur as a result of trauma to the eye. In many cases the cause remains uncertain. Systemic diseases such as Behçet’s disease and sarcoidosis can be associated with either acute or chronic uveitis. Ocular involvement is common in Behçet’s disease, and may cause severe uveitis.

The overall incidence of uveitis is estimated to be between 17 and 52.4 per 100,000 population equating to between 9,500 and 29,200 new cases per year in the UK. Posterior segment uveitis is less common than anterior uveitis and tends to be more severe; posterior segment uveitis accounts for around 1 in 5 cases. It is estimated that non-infectious posterior segment uveitis affects around 3 to 10 people per 100,000 in the European Union. This would equate to between 1,500 and 5,000 cases per year in England. The prevalence of Behçet’s disease in the UK is estimated at 0.64 per 100,000 population, which equates to approximately 400. Approximately 50-70% of patients with Behçet’s disease have uveitis and current estimates indicate that severe visual impairment occurs in 25% of involved eyes.

Gevokizumab is currently in three phase III clinical trials assessing its efficacy compared with placebo.
TARGET GROUP

- Uveitis: chronic; non-infectious.
- Uveitis: patients with Behçet’s disease.

TECHNOLOGY

DESCRIPTION

Gevokizumab (XOMA-052) is an anti-inflammatory humanized IgG2 monoclonal antibody that binds to interleukin-1β (IL-1β). It is intended for treatment of chronic, non-infectious uveitis, including that associated with Behçet’s disease. Binding to IL-1β blocks the activation of the IL-1 receptor preventing cellular signalling events that produce inflammation. Gevokizumab is intended for monthly subcutaneous (SC) dosing.

Gevokizumab is also in phase II development for rheumatoid arthritis and scleritis.

INNOVATION and/or ADVANTAGES

If licensed, gevokizumab will offer an alternative treatment option for this patient group.

DEVELOPER

SERVIER.

AVAILABILITY, LAUNCH OR MARKETING

Gevokizumab is a designated orphan drug in the EU and the USA for the treatment of chronic non-infectious uveitis.

Gevokizumab is currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Uveitis is inflammation of the uveal tract of the eye, which consists of the iris, the ciliary body and the choroid. Inflammation of nearby tissues, such as the retina, the optic nerve, and the vitreous humour may also occur. Uveitis may be classified by the anatomical location of the pathology: anterior, intermediate (vitritis), posterior (retina and choroid) or panuveitis. The course of uveitis may be acute, recurrent or chronic. Chronic uveitis can be differentiated from acute recurrent uveitis by its rate of progression and may be defined as active uveitis that persists longer than three months. Symptoms of uveitis can include: pain, redness, photophobia, headaches, visual floaters and decreased visual acuity. Non-infectious uveitis may be due to an underlying inflammatory condition, an autoimmune disorder or occur as a result of trauma to the eye. In many cases the cause remains uncertain. Systemic diseases such as Behçet’s disease and sarcoidosis can be associated with either acute or chronic uveitis. Ocular involvement is common in Behçet’s disease, and may cause severe uveitis.
Ocular inflammatory diseases are an important cause of blindness (BCVA\(^a\) < 20/400) or low vision (BCVA between 20/70 and 20/200) worldwide\(^8,9\). Non-infectious uveitis is frequently associated with a substantial burden of co-morbidity and with systemic disease in around one-third of cases\(^10\). Associated co-morbidities generally have a strong autoimmune component e.g. rheumatoid arthritis and psoriatic dermatologies\(^11\). It is often the extra-ocular symptoms of underlying inflammatory or autoimmune conditions which are the primary focus of treatment for these, with uveitis considered as a secondary manifestation\(^11\).

Chronic uveitis is associated with a high incidence of vision threatening complications such as cataract, macular oedema, and glaucoma\(^4\). Consequently uveitis is a leading cause of visual impairment in the UK\(^12\). In countries of the developed world, uveitis is the cause of about 1 in 10 cases of visual impairment\(^3\) with approximately 35% of patients reporting blindness or low vision in one eye\(^3,10,13\). Uveitis most commonly affects people aged 20 to 59, but may also occur in children\(^3\). Men and women are equally affected\(^1\). The existence of self-resolving forms of uveitis makes it difficult to ascertain its true incidence. However, the overall incidence is estimated to be between 17 and 52.4 per 100,000 population equating to between 9,500 and 29,200 new cases per year in the UK\(^3,11,14,15\). Posterior segment uveitis is less common than anterior uveitis and tends to be more severe; posterior segment uveitis accounts for around 1 in 5 cases\(^10\). It is estimated that non-infectious posterior segment uveitis affects around 3 to 10 people per 100,000 in the EU. This would equate to between 1,500 and 5,000 cases per year in England\(^16\).

The prevalence of Behçet’s disease in the UK is estimated at 0.64 per 100,000 population, which equates to approximately 400 patients\(^13\). Approximately 50-70% of patients with Behçet's disease have uveitis\(^3,12\) and current estimates indicate that severe visual impairment occurs in 25% of involved eyes\(^7\).

### RELEVANT GUIDANCE

#### NICE Guidance

No relevant guidance identified.

#### Other Guidance

- NHS Clinical Knowledge Summary. Uveitis (version 1.1). 2009\(^1\).
- Lyon F, Gale RG and Lightman S. Recent developments in the treatment of uveitis: an update. 2009\(^17\).
- Royal College of Ophthalmologists. Guidelines for Intravitreal Injections Procedure. 2009\(^18\).
- McCluskey PJ, Towler HMA and Lightman S. Management of Chronic Uveitis. 2000\(^4\).

\(^a\) BCVA: Best-corrected visual acuity.
EXISTING COMPARATORS and TREATMENTS

Corticosteroids are the mainstay of treatment for sight threatening posterior uveitis usually by periocular and occasionally intraocular steroid injection. However this is associated with significant systemic and ocular complications (such as glaucoma or cataract) if used at high doses over the longer term. Consequently, other immunosuppressive ‘corticosteroid sparing’ therapies may be used in an effort to reduce the corticosteroid dose required.

Current treatment options for non-infectious uveitis include:

- Cyclopegics eye drops – e.g. cyclopentolate or atropine sulphate.
- Corticosteroids:
  - Topical preparations – e.g. dexamethasone, prednisolone, rimexolone eye drops or fluorometholone eye drops (used in anterior uveitis).
  - Intravitreal injections – e.g. dexamethasone (used rarely in posterior uveitis), triamcinolone (unlicensed for this indication).
  - Intravitreal implant – e.g. dexamethasone (used in non-infectious posterior uveitis).
  - Systemic therapy – e.g. oral prednisolone or parenteral therapy (used in bilateral and/or severe cases of posterior or intermediate uveitis).
- Non-steroidal anti-inflammatory drugs (NSAIDs, not licensed for this indication in the UK) – e.g. diclofenac eye drops.
- Immunosuppressive drugs (not licensed for this indication in the UK):
  - Antimetabolites – e.g. azathioprine, mycophenolate mofetil (or mycophenolic acid) or methotrexate.
  - Leukocyte signalling inhibitors – e.g. ciclosporin or tacrolimus.
  - Tumour necrosis factor (TNF)-α inhibitors – e.g. infliximab, adalimumab or golimumab are considered in patients who fail to respond to one or two ‘classic’ immunosuppressive agents (such as antimetabolites) or leukocyte signalling inhibitors.
  - Alkylating agents – e.g. cyclophosphamide or chlorambucil (used for severe vision-threatening conditions).

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>EYEGUARD™-A, NCT01684345; gevokizumab vs placebo; phase III.</th>
<th>EYEGUARD™-C, NCT01747538; gevokizumab vs placebo; phase III.</th>
<th>EYEGUARD™ B, EudraCT Number: 2012-001125-27; gevokizumab vs placebo; phase III.</th>
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<tr>
<td>Sponsor</td>
<td>Xoma (US) LLC.</td>
<td>Xoma (US) LLC.</td>
<td>Servier.</td>
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<td>Source of information</td>
<td>Trial registry[^21].</td>
<td>Trial registry[^22].</td>
<td>Trial registry[^23].</td>
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<tr>
<td>Location</td>
<td>USA only.</td>
<td>USA only.</td>
<td>EU (inc UK), and other countries.</td>
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</tbody>
</table>

[^21]: Expert clinical opinion.
Participants
n=300 (planned); aged ≥18 years; diagnosis of non-infectious intermediate, posterior, or pan-uveitis in at least one eye; active uveitic disease in at least one eye; on at least one of the following stable treatment regimens: oral corticosteroids, systemic immunosuppressant medication.

n=300 (planned); aged ≥18 years; diagnosis of non-infectious intermediate, posterior, or pan-uveitis in at least one eye; controlled uveitic disease in both eyes; on stable dose of oral corticosteroids in combination with selected immunosuppressive therapy.

n=80 (planned); aged ≥18 years; diagnosed with Behçet’s disease associated uveitis with ocular involvement of the posterior segment; stable background treatment regimen of oral corticosteroid and immunosuppressive treatment; without severe cataract or severe posterior capsular opacification.

Schedule
Not reported by company.

Not reported by company.

Not reported by company.

Follow-up
Not reported by company.

Not reported by company.

Not reported by company.

Primary outcome/s
Responders at day 56.

Occurrence of uveitic disease to day 168.

Time to first ocular exacerbation.

Secondary outcome/s
Not reported. Quality of life measurements not reported by company.

Time to first occurrence of uveitic disease. Quality of life measurements not reported by company.

Ocular exacerbations; visual acuity. Quality of life measurements not reported by company.

Expected reporting date
Estimated study completion date Sept 2015.

Estimated study completion date Feb 2015.

Estimated study completion date Sept 2016.

Trial
ISRCTN15180871; gevokizumab; phase II.

Sponsor
Servier.

Status
Ongoing.

Source of information
Trial registry, manufacturer.

Location
South Korea, Tunisia and Turkey.

Design
Randomised, open-label.

Participants
n=21 (planned); aged 18 to 80 years; patients with uveitis associated with Behçet’s disease; stable regimen of oral corticosteroids and immunosuppressive treatment; without severe cataract.

Schedule
Not reported by company.

Follow-up
Active treatment for 1 year.

Primary outcome/s
Safety (adverse events (AEs); vital signs; laboratory values; ECG and X-ray).

Secondary outcome/s
Pharmokinetics; ophthalmological assessments. Quality of life measurements not reported by company.

Expected reporting date
Estimated study completion date May 2013.

ESTIMATED COST and IMPACT

COST

The cost of gevokizumab for this indication is not yet known. The cost of a single 700µg dexamethasone intravitreal implant (Ozurdex) is £870. However this figure does not include of the cost of the surgical implantation.
**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**
- ☐ Reduced mortality/increased length of survival
- ☑ Reduced symptoms or disability
- ☐ Other:
- ☑ No impact identified

**Impact on Services**
- ☐ Increased use of existing services
- ☑ Decreased use of existing services: by comparison with Ozurdex where a surgical procedure is needed to place and remove the implant. However, use of gevokizumab will require increased monitoring of patients for as long as they are on this drug, including blood or other tests at regular intervals. At present, this is undertaken by nursing staff trained in immunosuppression in rheumatology, or less often, ophthalmology departments.
- ☐ Re-organisation of existing services
- ☐ Other:
- ☑ Need for new services
- ☑ None identified

**Impact on Costs**
- ☐ Increased drug treatment costs
- ☑ Reduced drug treatment costs
- ☐ Other increase in costs:
- ☑ Other reduction in costs:
- ☑ Other: uncertain unit cost compared to existing treatments.
- ☑ None identified

**Other Issues**
- ☑ Clinical uncertainty or other research question identified: There are currently no effective ways of predicting severity, and therefore outcome of disease in chronic, non-infectious uveitis. Further research in this area would be useful. In addition, the increased use of intravitreal therapies requires the rigour of randomised trials in order to describe their place in treatment. This is important as the local side-effects of intravitreal treatment (eg, cataract/glaucoma) are relatively easy to manage, whereas the long-term side effects from systemic immunosuppression are more difficult, particularly for ophthalmologists.
- ☑ None identified

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**REFERENCES**


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*Expert clinical opinion.*
10 NIHR Horizon Scanning Centre. Intravitreal sirolimus (Opsiria) for chronic non-infectious posterior segment uveitis – first or second line. University of Birmingham, January 2013. http://www.hsc.nihr.ac.uk