Avacopan is a new drug to treat anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (inflammation of the blood vessels). ANCA-associated vasculitis is a type of autoimmune inflammation caused by abnormal antibodies that attack the body’s own cells. Avacopan is taken by mouth and some studies have suggested that it may help to treat ANCA-associated vasculitis by reducing the damage caused by inflammation.
TARGET GROUP

- Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) – first and subsequent line.

TECHNOLOGY

DESCRIPTION

Avacopan (CCX-168) is a small molecule, complement C5a receptor inhibitor. Chemoattractant receptors, such as C5aR, are receptors for complement proteins involved in specific inflammatory responses. C5a is believed to be a potent chemoattractant underlying the inflammation-induced damage in certain autoimmune disorders, including AAV, thus inhibitors of C5aR have a therapeutic potential. In clinical trials, avacopan was administered orally, at 10mg or 30mg twice daily for 12 weeks.

Avacopan is also in phase II clinical trials for haemolytic uraemic syndrome and IgA nephropathy.

INNOVATION and/or Advantages

If licensed, avacopan will provide an alternative, oral treatment option to oral glucocorticoids for patients with AAV. Expert opinion suggests avacopan has the potential advantages of superior efficacy with faster remission and reduced end-organ damage, and reduced glucocorticoid-related toxicity.

DEVELOPER

ChemoCentryx.

AVAILABILITY, LAUNCH OR MARKETING

Avacopan is a designated orphan drug in the EU and USA for AAV and was awarded PRIME status for AAV by the EMA in May 2016.

PATIENT GROUP

BACKGROUND

Vasculitis is a group of rare diseases characterised by inflammatory cell infiltration and necrosis of blood vessel walls. The severity of vasculitis is related to the size, site and number of vessels affected. The major vasculitis subgroup with small vessel involvement is AAV. There are three subtypes of AAV: microscopic polyangitis (MPA), granulomatosis with polyangitis (GPA, formerly known as Wegener’s granulomatosis), and eosinophilic granulomatosis with polyangitis (EPGA, formerly known as Churg-Strauss syndrome). AAV is a very variable disease group which is unpredictable and potentially life threatening. Symptoms will vary, being dependent on which organs are affected. General symptoms include: tiredness, weakness, loss of appetite, weight loss and fever. Risk factors include
genetic factors, with AAV varying in phenotype between ethnic groups\(^a\). Heavy silica exposure is the only environmental factor that has been causally linked with AAV. Typically the disease is preceded by a prodromal phase of several months of infective-type symptoms\(^a\).

### CLINICAL NEED and BURDEN OF DISEASE

In England, the annual incidence of AAV is 20 per million population (MPA 5.9 per million, GPA 11.3 per million, EGPA 2.8 per million) and the prevalence is approximately 250 per million\(^6\). The peak age at diagnosis is 65-74 years\(^6\), with a similar gender distribution\(^a\). Untreated, AAV progresses rapidly; infections and active vasculitis account for most deaths in the first year after diagnosis\(^2\). However, modern therapy has improved the prognosis from conditions with high mortality to chronic diseases with a relapsing and remitting course\(^2\). The 5-year survival rates for MPA, GPA and EGPA are estimated at 45-76%, 74-91% and 60-97% respectively\(^4\).

In 2014-15, there were 734 hospital admissions in England for other specified disorders of arteries and arterioles (ICD-10 I77.8), accounting for 1,018 finished consultant episodes and 4,299 bed days\(^7\). In 2014, 20 deaths were registered in England and Wales\(^8\), although expert opinion suggests this figure is likely to be significantly underestimated\(^a\). It is estimated that approximately 480-948 people in England diagnosed with AAV will require rituximab therapy (including maintenance treatment) each year\(^6\).

### PATIENT PATHWAY

#### RELEVANT GUIDANCE

**NICE Guidance**


**NHS England Policies and Guidance**


**Other Guidance**

- European League Against Rheumatism. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. 2016\(^4\).
- British Society for Rheumatology. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. 2014\(^9\).

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\(^a\) Expert personal opinion.
CURRENT TREATMENT OPTIONS

The treatment of AAV consists of two phases: remission induction and maintenance of remission. Treatment depends on the severity and extent of organ involvement. Current treatment options for AAV include:

- For remission/induction or major relapse of organ- or life-threatening disease – combination therapy with glucocorticoids and either cyclophosphamide or rituximab.
- For remission induction of non-organ-threatening AAV – combination therapy with glucocorticoids and either methotrexate or mycophenolate mofetil.
- For remission maintenance – combination therapy with low-dose glucocorticoids and either azathioprine, rituximab, methotrexate or mycophenolate mofetil.
- For patients refractory to remission-induction therapy, a switch from cyclophosphamide to rituximab or from rituximab to cyclophosphamide is recommended.
- For patients with severe renal impairment or diffuse alveolar haemorrhage, plasma exchange may be considered.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01363388; avacopan vs placebo; phase II.</th>
<th>NCT02222155, avacopan vs placebo; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>ChemoCentryx</td>
<td>ChemoCentryx</td>
</tr>
<tr>
<td>Status</td>
<td>Complete</td>
<td>Complete</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry</td>
<td>Trial registry</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK)</td>
<td>USA and Canada</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
<td>Randomised, placebo-controlled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=67 (planned); aged ≥18 years; AAV; newly diagnosed or relapsed.</td>
<td>n=42 (planned); aged ≥18 years; AAV; newly diagnosed or relapsed.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to avacopan or placebo, oral, twice daily for 12 weeks. Dose not reported.</td>
<td>Randomised to avacopan 10mg or 30mg, or placebo, all oral, twice daily for 12 weeks. All arms in combination with standard of care.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment for 12 weeks; follow-up not reported.</td>
<td>Active treatment for 12 weeks; follow-up not reported.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Safety; efficacy.</td>
<td>Birmingham Vasculitis Activity Score (BVAS).</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Systemic corticosteroid use.</td>
<td>eGFR; haematuria; albuminuria; urinary monocyte chemoattractant protein-1 (MCP-1).</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Not reported.</td>
<td>Not reported.</td>
</tr>
</tbody>
</table>

ESTIMATED COST and IMPACT

COST

The cost of avacopan is not yet known. The costs of one other selected current treatment for AAV is summarised in the following table:
Horizon Scanning Research & Intelligence Centre

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Treatment cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab (MabThera)</td>
<td>2g, delivered at 1g IV, two weeks apart</td>
<td>£3,492 per course</td>
</tr>
</tbody>
</table>

### IMPACT - SPECULATIVE

#### Impact on Patients and Carers

- Reduced mortality/increased length of survival
- Other: Reduced symptoms or disability
- No impact identified

#### Impact on Health and Social Care Services

- Increased use of existing services
- Decreased use of existing services: potential steroid-sparing oral treatment option.
- Re-organisation of existing services
- Need for new services
- Other: None identified

#### Impact on Costs and Other Resource Use

- 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:
- None identified

### REFERENCES


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^ NICE recommend 4 doses at 375mg/m², however in England, a lower total dose is usually administered^b.