**Avacopan in addition to standard of care for ANCA-associated vasculitis**

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<thead>
<tr>
<th>NIHRIO ID</th>
<th>24160</th>
<th>NICE ID</th>
<th>10023</th>
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<tbody>
<tr>
<td>Developer/Company</td>
<td>ChemoCentryx and Vifor Pharma UK Ltd</td>
<td>UKPS ID</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Licensing and market availability plans**

Current in phase III trial

**SUMMARY**

Avacopan is in clinical development, in addition to current standard of care, for inducing and sustaining remission in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis (ANCA-associated vasculitis). ANCA-associated vasculitis is a potentially fatal autoimmune condition characterised by damage to, and inflammation of, small blood vessels commonly in the kidneys, respiratory tract or the skin. Current treatment typically includes glucocorticoids in addition to other therapies to induce and sustain remission. Long-term treatment with glucocorticoids is however associated with increased toxicity, harmful side-effects and negative impact on patients’ quality of life.

Avacopan is an orally-administered medicinal product that targets specific proteins that contribute to the inflammation of small blood vessels in ANCA-vasculitis. Avacopan has been shown to be of benefit as an alternative to glucocorticoids for the induction of remission in ANCA-associated vasculitis. It has fewer side-effects than glucocorticoids, and may also improve the preservation of kidney function. If licensed, avacopan in addition to standard of care therapies could offer an option for inducing and sustaining remission in patients with ANCA-associated vasculitis.
PROPOSED INDICATION

For inducing and sustaining remission in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis (ANCA-associated vasculitis) including Granulomatosis with polyangiitis (GPA) and Microscopic polyangiitis (MPA).  

TECHNOLOGY

DESCRIPTION

Avacopan is an orally-administered complement inhibitor, specifically targeting the C5a receptor 1 (C5aR1), which binds the complement fragment C5a. C5a is one of a group of proteins in the blood (the ‘complement system’) that form part of the immune system. When C5a attaches to C5aR it attracts and activates certain immune cells called neutrophils, which are thought to contribute to the inflammation of small blood vessels in ANCA-vasculitis.

Avacopan (CCX168) is in clinical development, in addition to current standard of care, for inducing and sustaining remission for patients with ANCA-associated vasculitis (GPA and MPA). In the phase III trial (ADVOCATE; NCT02994927), avacopan is administered orally at 30mg twice daily in combination with rituximab intravenous (IV) infusion for 4 weeks or cyclophosphamide (IV or oral) for 12 weeks. The trial duration is up to one year. The trial focuses on the induction of remission up to 6 months and then sustaining of remission until 12 months.

INNOVATION AND/OR ADVANTAGES

Glucocorticoids (usually 15mg prednisolone) in combination with other standard of care therapies are the recommended treatment to induce and maintain remission in patients with ANCA-associated vasculitis. Maintenance therapy should continue for at least 24 months following successful disease remission, although patients in continual remission for at least one year should be considered for tapering of glucocorticoid treatment. However, higher cumulative glucocorticoid doses are associated with increased toxicity and damage accumulation, increased risk of infection, metabolic syndrome, bone loss, and an overall negative impact on health-related quality of life.

Avacopan has been shown to be non-inferior to high dose glucocorticoids in remission induction in ANCA-associated vasculitis. It is thought that avacopan may be an alternative to the use of oral glucocorticoids, with a lower incidence of adverse effects which are common in patients receiving the high doses used for long periods in this condition, and may have additional benefits including improved preservation of renal function.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Avacopan does not currently have Marketing Authorisation in the EU/UK for any indication.

Avacopan is at pre-registration in EU for the treatment of patients with ANCA-associated vasculitis.

Avacopan is also in phase II clinical trials for the treatment of complement 3 glomerulopathy (C3G) and atypical haemolytic uremic syndrome (aHUS).

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a Information provided by company
b Information provided by company
Avacopan has received the following regulatory designations/awards:

- Orphan drug in EU in November 2014 for the treatment of microscopic polyangiitis and granulomatosis with polyangiitis
- PRIME status by EMA in May 2016 for the treatment of ANCA-associated vasculitis
- Orphan drug in USA in June 2014 for the treatment of ANCA-associated vasculitides, microscopic polyangiitis and Churg-Strauss syndrome

DISEASE BACKGROUND

According to the 2012 International Chapel Hill consensus conference on the nomenclature of vasculitides, ANCA-associated vasculitis is an umbrella term for several systemic diseases with characteristics of small blood vessel inflammation which might target almost every organ with the risk of fatal outcomes. There are three different disease entities: granulomatosis with polyangiitis (GPA; Wegener’s granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). ANCA are directed against the granule proteins myeloperoxidase (MPO) or proteinase 3 (PR3), and there is evidence that ANCA are pathogenic and cause effector functions in neutrophils and monocytes, leading to subsequent tissue damage via interaction with endothelial cells. There is evidence that both genetic susceptibility and environmental exposures contribute to the aetiology of ANCA-associated vasculitis, and infections may also be a trigger. The incidence of ANCA-associated vasculitis increases with age, and the peak age of onset is between 60 and 70 years.

ANCA-associated vasculitis frequently involve multiple organ systems: most commonly the kidneys, ENT/respiratory tract, skin and nervous system are affected. The condition can cause different symptoms depending on what organ or part of the body is involved. For example, when blood vessels in the skin are affected it can cause a rash, or when blood vessels in the kidney are affected it can cause blood and protein to leak into the urine as well as kidney damage. Generalised symptoms include fever or night sweats, body aches, joint and muscle pain, decreased appetite and weight loss.

Without treatment ANCA-associated vasculitis is usually fatal, and not everyone responds to treatment. The likelihood of relapse varies according to disease, but is highest in GPA. Each relapse carries a risk that additional critical organ damage will occur, leading to an irreversible deterioration in health. Kidney involvement is very common, occurring more frequently in MPA (90%) and in GPA (70%). Some patients may have normal or only very mild reduction in kidney function, but most patients with renal vasculitis have chronic kidney disease (CKD), which is associated with high blood pressure and risk of cardiovascular disease. Approximately 20% of patients with renal vasculitis develop end stage renal disease within a few years after diagnosis, meaning they need dialysis and perhaps a kidney transplant.

CLINICAL NEED AND BURDEN OF DISEASE

ANCA-associated vasculitis has an annual incidence of 20 persons per million, and a prevalence of 200 persons per million. Using the latest population estimates for England and Wales (2017) this equates to an annual incidence of 1,175 persons and a prevalence of 11,750 persons.

According to a 2017 study, it is estimated that there are 700 new cases of GPA each year in the UK, of whom 95 will die within 12 months. It is also estimated that there were 8,750 people living with GPA in the UK in 2016. On average, 80% of those treated will be alive at two years, and 20% of these survivors will have significant renal disease. Up to 50% of patients will relapse within 5 years,
even with maintenance immunosuppression. Relapse is often associated with significantly increased NHS costs e.g. hospitalisation, and both the costs (drug and day case activity) and infection risk from steroids and immunosuppression of remission re-induction. Significant costs also accrue at relapse from the accumulation of further organ damage, particularly if this leads to further renal damage and risk of renal replacement therapy.  

The burden of disease relates to both the acute vasculitis phase (when patients have significant morbidity and are usually admitted to hospital), and chronic organ damage due to both vasculitis activity and the impact of treatment in particular glucocorticoids. There is significant long-term damage relating to hearing loss, infection risk, renal disease, osteoporotic fractures and renal failure as well as higher long-term mortality risk. In England in 2017/18 there were 2,901 finished consultant episodes (FCEs) with a primary diagnosis of ICD-10 code M313 (GPA), and 8,038 FCEs with diagnosis in any position, indicating that around 65% of hospital admissions for patients with GPA are to treat conditions other than GPA.  

### PATIENT TREATMENT PATHWAY

**PATIENT PATHWAY**

The management of ANCA-associated vasculitis involves three phases: remission induction, remission maintenance, and treatment of relapse. At regular intervals it is essential to formally assess and define disease activity and damage status using a formal instrument such as the Birmingham Vasculitis Activity Score (BVAS) so that an accurate ascertainment of remission, refractory disease or relapse can be documented in every patient.

### CURRENT TREATMENT OPTIONS

Guidelines from British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) recommend:

- All patients with newly-diagnosed ANCA-associated vasculitis should be assessed for treatment with glucocorticoids and cyclophosphamide or rituximab. Glucocorticoids are usually given as daily oral prednisolone. It is recommended that the aim is to rapidly reduce glucocorticoids to 15mg prednisolone at 12 weeks.

- Following successful remission, cyclophosphamide should be withdrawn and substituted with either azathioprine or methotrexate.

- Azathioprine intolerance is relatively common. Methotrexate is renally excreted, therefore it should be used cautiously in those with impaired renal function and the dose adjusted to CKD stage. Mycophenolate mofetil or leflunomide may be used as alternatives for intolerance or lack of efficacy of azathioprine or methotrexate.

- Rituximab may also be used as maintenance therapy, and re-treatment can be decided based on fixed-interval regimens or evidence of relapse. The recommended rituximab regimen uses 1g every 4-6 months for two years.
 Patients should continue maintenance therapy for at least 24 months following successful disease remission. Patients with GPA or patients who remain PR3-ANCA positive should continue immunosuppression for up to 5 years.

 Patients with good disease control may not need indefinite therapy. Higher cumulative glucocorticoid doses are associated with increased toxicity and damage accumulation.

 Patients in continual remission for at least one year on maintenance therapy should be considered for tapering of glucocorticoid treatment. Following glucocorticoid withdrawal, other immunosuppressive therapy may be withdrawn after 6 months.

**PLACE OF TECHNOLOGY**

If licenced, avacopan in addition to standard of care therapies may offer an option for induction remission and sustained remission for patients with ANCA-associated vasculitis (GPA and MPA). It may potentially be used as an alternative to high dose glucocorticoids to induce and sustain remission.

**CLINICAL TRIAL INFORMATION**

<table>
<thead>
<tr>
<th>Trial</th>
<th>ADVOCATE, <a href="https://clinicaltrial.gov/ct2/show/NCT02994927">NCT02994927</a>, EudraCT-2016-001121-14; avacopan vs prednisone, both in combination with rituximab or cyclophosphamide, followed by azathioprine; phase III</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>ChemoCentryx</td>
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<tr>
<td>Status</td>
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<tr>
<td>Source of Information</td>
<td>Trial registry², trial website²⁰, abstract¹</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada, Australia, New Zealand and Japan</td>
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<tr>
<td>Design</td>
<td>Randomised, active-controlled</td>
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<tr>
<td>Participants</td>
<td>n=300; age 18 yrs and older (but age 12-17 yrs may be enrolled where approved by regulatory agencies); clinical diagnosis of granulomatosis with polyangiitis (Wegener’s) or microscopic polyangiitis; newly diagnosed or relapsed ANCA-associated vasculitis where treatment with cyclophosphamide or rituximab is needed; positive test for anti-PR3 or anti-MPO; at least 1 major item, or at least 3 non-major items, or at least the 2 renal items of proteinuria and haematuria on BVAS</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to avacopan 30mg twice daily orally administered; or prednisone 60mg/day tapered to 0mg over 21 wks orally administered; both in combination with rituximab IV for 4 wks or cyclophosphamide (IV or oral) for 12 wks, followed by azathioprine orally administered.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment for 12 mths and follow-up period 2 mths</td>
</tr>
</tbody>
</table>
| Primary Outcomes | • Proportion of pts achieving disease remission assessed by Birmingham Vasculitis Activity Score (BVAS) at wk 26  
• Proportion of pts achieving sustained disease remission assessed by BVAS at wk 52 |
| Secondary Outcomes | • Pt incidence of treatment-emergency serious adverse events, adverse events, and withdrawals due to adverse events [Time frame: 60 wks]  
• Glucocorticoid-induced toxicity as measured by the Glucocorticoid Toxicity Index [Time frame: 26 wks]  
• Response rapidity: remission assessed by BVAS at wk 4 |
Time frame 52 wks:
- Change in health-related quality of life based on SF-36v2 component and domain scores and EuroQOL-5D-5L visual analogue scale and index
- Change from baseline in estimated glomerular filtration rate (eGFR)
- Change from baseline in urinary albumin:creatinine ratio (UACR)
- Change from baseline in urinary monocyte chemoattractant protein-1 (MCP-1):creatinine ratio
- Change from baseline in Vasculitis Damage Index (VDI)

### Key Results

**Adverse effects (AEs)**

- Expected reporting date

**Expected reporting date**

Primary completion date reported as June 2019

### Trial

**Trial**

CLEAR, NCT01363388, EudraCT-2011-001222-15, ISRCTN53663626, UKCRN10379; avacopan vs placebo; phase II

**Sponsor**

ChemoCentryx

**Status**

Published

**Source of Information**

Publication⁹, abstract¹¹,²², trial registry²³

**Location**

10 EU countries, incl UK

**Design**

Randomised, placebo-controlled

**Participants**

n=67; aged 18 yrs and older; clinical diagnosis of granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis or renal limited vasculitis; newly diagnosed or relapsed AAV where treatment with cyclophosphamide or rituximab would be required; positive indirect immunofluorescence (IIF) test for P-ANCA or C-ANCA, or positive ELISA test for anti-PR3 or anti-MPO at screening; estimated glomerular filtration rate (eGFR) ≥ 20mL/min; have at least one "major" item, or at least 3 non-major items, or at least 2 renal items on the BVAS version 3

**Schedule**

Randomised to avacopan 30mg twice daily without prednisone; avacopan 30mg twice daily and low dose prednisone (20mg, tapered); full dose prednisone (60mg, tapered); all in combination with rituximab or cyclophosphamide.

**Follow-up**

Active treatment for 84 days, follow-up 85 days

### Primary Outcomes

**Time frame 169 days:**

- Safety of avacopan, assessments including adverse events, physical examination abnormalities, vital signs and clinical laboratory tests (incl blood chemistry, haematology and urinalysis)
- Efficacy of avacopan, assessed by BVAS

### Secondary Outcomes

**Time frame 169 days:**

- Systemic corticosteroid use based on total oral corticosteroid dose and duration of oral corticosteroid use

### Key Results

Before treatment, levels of C3a, C5a, sC5b-9 and properdin were significantly elevated in ANCA-associated vasculitis patients compared to matched healthy controls (geomean [95%], C3a, 67.2 [57.5–78.7] vs 23.2 [16.9–31.9] ng/mL, p<0.001; C5a, 7.55 [6.50–8.78] vs 5.19 [3.87–6.95] ng/mL, p<0.05; sC5b-9, 241(222–262) vs 155(136–178) ng/mL, p<0.001; Properdin, 18.4 [16.9–20.0] vs 13.1 [11.4–15.6] µg/mL, p<0.001). In subjects treated with full dose prednisone, levels of Bb, C3a, and C5a decreased significantly on day 8 and 29 rising again at day 85, coincident with tapering. Consistent with its mode of
action (inhibition of C5aR1, the receptor at the terminus of the complement cascade), avacopan did not impact circulating complement levels. There were no changes from baseline in mean plasma sC5b-9 or properdin levels in any treatment group.

The primary efficacy measure was the proportion of patients achieving a ≥50% reduction in BVAS by wk 12 and no worsening in any body system. Clinical response at wk 12 was achieved in 14 of 20 (70.0%) control pts, 19 of 22 (86.4%) pts in the avacopan plus reduced-dose prednisone group (difference from control 16.4%; two-sided 90% confidence limit, −4.3% to 37.1%; P=0.002 for noninferiority), and 17 of 21 (81.0%) pts in the avacopan without prednisone group (difference from control 11.0%; two-sided 90% confidence limit, −11.0% to 32.9%; P=0.01 for noninferiority).

Adverse effects (AEs)

Adverse events occurred in 21 of 23 (91%) control pts, 19 of 22 (86%) pts in the avacopan plus reduced-dose prednisone group, and 21 of 22 (96%) pts in the avacopan without prednisone group.

<table>
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<th>Trial</th>
<th>CLASSIC, NCT02222155, ISRCTN19848432; avacopan vs placebo; phase II</th>
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<td>Sponsor</td>
<td>ChemoCentryx</td>
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<td>Abstract²⁴,²², trial registry²⁵</td>
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<td>Design</td>
<td>Randomised, placebo-controlled</td>
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<td>Participants</td>
<td>n=42; aged 18 yrs and older; clinical diagnosis of granulomatosis with polyangiitis (Wegener’s), microscopic polyangiitis or renal limited vasculitis; newly diagnosed or relapsed ANCA-associated vasculitis where treatment with cyclophosphamide or rituximab would be required; positive indirect immunofluorescence (IIF) test for P-ANCA or C-ANCA, or positive ELISA test for anti-PR3 or anti-MPO at screening; estimated glomerular filtration rate (eGFR) ≥ 20mL/min; have at least one &quot;major&quot; item, or at least 3 non-major items, or at least 2 renal items on the BVAS version 3</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to avacopan 10mg twice daily; avacopan 30mg twice daily; placebo twice daily; all in combination with chronic high doses of prednisone plus either rituximab or cyclophosphamide (standard of care (SOC) treatment)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment for 12 wks, follow-up not reported</td>
</tr>
<tr>
<td>Primary Outcomes</td>
<td>BVAS [Time frame: 12 wks]</td>
</tr>
</tbody>
</table>
| Secondary Outcomes | Time frame: 12 wks:  
  - eGFR  
  - Haematuria  
  - Albuminuria  
  - Urinary monocyte chemoattractant protein-1 (MCP-1) |
| Key Results | Three grps: placebo + SOC (n=13); 10mg avacopan twice daily + SOC (n=13); 30mg avacopan twice daily + SOC (n=16). Response at wk 12, based on BVAS, was achieved in 10, 11, and 12 pts, respectively, in each grp. Early remission (BVAS = 0 at wk 4) was achieved in 2, 1, and 5 pts, respectively. eGFR mean change from baseline to wk 12 was 0.8, -0.8, and 3.1 mL/min/1.73 m², respectively, in each group. |
Across CLEAR and CLASSIC trials, avacopan showed significantly more rapid and superior reduction in proteinuria; a rapid, numerically superior BVAS reduction; superior reduction of urinary kidney inflammation markers; stabilization of eGFR absent of steroids; attenuated VDI, significantly more rapid normalization of blood neutrophils than SOC. Pt-reported outcomes (EuroQol, SF-36) significantly improved baseline to wk 12 in avacopan group; significantly superior to SOC. Remarkably, QOL assessment at wk 12 of avacopan therapy nearly matched values from healthy, general population controls.

| Adverse effects (AEs) | Avacopan was found to be safe when added to SOC high-dose glucocorticoids (prednisone) and either rituximab or cyclophosphamide. A total of 7 pts had serious adverse events, 2 of 13 patients in the placebo + SOC grp, 2 of 13 in the 10mg avacopan + SOC grp, and 3 of 16 in the 30mg avacopan grp. These included 4 infection-related SAEs: toe gangrene (1), cellulitis and skin abscesses (1), and sepsis and urinary tract infection (1 each) in the three grps, respectively. Total AEs occurred in 13, 11, and 15 patients in the three grps, respectively. |

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**ESTIMATED COST**

The cost of avacopan is not yet known.

**ADDITIONAL INFORMATION**

ChemoCentryx is the developer of this product, but Vifor Pharma have commercialisation rights outside US and China.8

Vifor Pharma did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

**RELEVANT GUIDANCE**

**NICE GUIDANCE**

- NICE technology appraisal in development. Rituximab for maintenance treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1320]. Expected publication date to be confirmed.
- NICE technology appraisal in development. Avacopan for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [ID1178]. Expected publication date to be confirmed.
- NICE technology appraisal in development. Mepolizumab for treating eosinophilic granulomatosis with polyangiitis [ID1186]. Expected publication date to be confirmed.
NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE


OTHER GUIDANCE

- British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR). BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. 2014.5
- European League Against Rheumatism (EULAR) and European Renal Association - European Dialysis and Transplant Association (ERA-EDTA). EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. 2016.26

REFERENCES


NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.