Thrombotic thrombocytopenic purpura is a rare blood disorder that causes blood clots in small blood vessels. These tiny blood clots cause damage to internal organs and red blood cells.

Caplacizumab is a drug that is being given for the treatment of thrombotic thrombocytopenic purpura. The drug is injected under the skin and given alongside the current treatment of plasma exchange.

Studies are currently ongoing to see how well caplacizumab works and how safe it is to use. If caplacizumab is licensed for use in the UK, it could provide a new treatment option for patients with thrombotic thrombocytopenic purpura.

NIHR HSRIC ID: 6966
TARGET GROUP

- Thrombotic thrombocytopenic purpura (TTP): acquired; acute phase – adjunctive.

TECHNOLOGY

DESCRIPTION

Caplacizumab (ALX-0081; anti-von Willebrand factor nanobody; anti-vWF inhibitor) is a bivalent anti-von Willebrand factor humanised nanobody (single domain antibody) for the prevention of thrombus formation in high-shear blood vessels. It inhibits the interactions between von Willebrand factor, collagen and platelets to prevent the earliest stages of thrombus formation. It is intended to treat patients suffering an acute episode of TTP by more rapidly curtailing ongoing microvascular platelet thrombosis when administered in addition to standard of care treatment. In the phase III clinical trial, caplacizumab is administered as an initial 10mg IV dose followed by daily 10mg SC injections for the duration of daily plasma exchange and 30 days thereafter. Extension of treatment may be considered in patients where the underlying disease has not yet resolved for a maximum period of 6 months. Caplacizumab does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, caplacizumab will offer an additional novel treatment option for patients with TTP who are receiving plasma exchange (PEX), a group who currently have no other specifically licensed therapies available.

DEVELOPER

Ablynx NV.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

TTP is a rare blood disorder characterised by the formation of platelet aggregates in small blood vessels resulting in red cell fragmentation and thrombocytopenia (thrombotic microangiopathy). It has an acute clinical onset with a classical pentad of symptoms and signs, although not all are always present - neurological changes, pyrexia, renal dysfunction, thrombocytopenia, and fragmented red cells. Surprisingly, major bleeding problems are rare but petechiae are common. Neurological symptoms can include from headache, confusion, altered consciousness, coma, seizures, hemiparesis and visual disturbances. The commonest cause of early death is due to the formation of platelet aggregation in the coronary circulation leading to arrhythmia, infarction and cardiac arrest.
TTP is caused by the inactivation of the enzyme ADAMTS13, a metalloprotease which breaks down large von Willebrand factor multimers. When ADAMTS13 levels are very low, the ultra-large von Willebrand factor multimers can under high shear conditions initiate platelet aggregation, causing a thrombotic microangiopathy. ADAMTS13 deficiency can occur either due to an inherited genetic mutation (inherited TTP) or through antibody – mediated destruction (acquired TTP). Acquired TTP can be associated with pregnancy, HIV, other autoimmune conditions such as systemic lupus erythematosus, and some medicines such as ticlopidine, clopidogrel, ciclosporine A, and hormone therapy. Other forms of TTP can also occur in cancer patients or after bone marrow transplants.

**NHS or GOVERNMENT PRIORITY AREA**
- No relevant guidance identified.

**CLINICAL NEED and BURDEN OF DISEASE**
TTP has an annual incidence of 6 cases per million in the UK and is more common in females than males. Acquired TTP is far more common than congenital TTP, and accounts for over 95% of all cases. Patients may suffer from only one acute TTP episode; however, relapses have been reported in 30-40% of patients.

In 2014-15, there were 437 hospital admissions for thrombotic microangiopathy (ICD-10 M31.1), resulting in 1,539 bed days and 535 finished consultant episodes. In 2014, there were 30 deaths from thrombotic microangiopathy in England and Wales. Mortality exceeds 90% in patients who do not receive PEX treatment; however, with treatment, this rate decreases to approximately 15%.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**
- No relevant guidance identified.

**Other Guidance**

**CURRENT TREATMENT OPTIONS**
Daily PEX, which allows removal of autoantibody and repletes ADAMTS13, is the main treatment employed for acute episodes of TTP. Increasingly, this is combined with rituximab to provide immunosuppression. Guidelines recommend that PEX should be started with three 1.5 x plasma volume (PV) exchanges using solvent/detergent-treated plasma. The

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* Expert personal opinion
volume of PEX can be reduced to 1.0 x PV when the clinical condition and laboratory test results have stabilised. Intensification in frequency or volume of PEX procedures should be considered in severe cases\(^6\). Daily PEX should be continued for a minimum of 2 days after platelet count has reached >150 x 10\(^9\)/L. If PEX is not immediately available, fresh frozen plasma at 30mL/kg should be given until treatment with PEX can commence\(^3,6\). Once the platelet count is >50 x 10\(^9\)/L, low molecular weight heparin and aspirin, at a dose of 75mg once daily, should be commenced to prevent hospital-acquired venous thromboembolism\(^6\). Packed red cells may be transferred where necessary to correct anaemia\(^6\).

Guidelines also recommend the use of intravenous daily methylprednisolone (1g/day for 3 consecutive days) or high dose oral prednisolone (1mg/kg/day for 3 consecutive days) in combination with PEX as an initial treatment\(^6\).

For patients with refractory or relapsing immune-mediated TTP, rituximab (unlicensed for this indication) should be offered at a recommended dose of 375mg/m\(^2\) weekly for 4 weeks\(^6\).

Supportive care for organ damage may also be required\(^3\).

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>HERCULES, NCT02553317, ALX0681-C301 2015-001098-42; aged 18 years and over; caplacizumab vs placebo; phase III.</th>
<th>TITAN, NCT01151423, ALX-0681-2.1/10, 2010-019375-30; aged 18 years and over; caplacizumab vs placebo; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Ablynx NV.</td>
<td>Ablynx NV.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Completed.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Company, trial registry(^1).</td>
<td>Publication(^12), company, trial registry(^13).</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, and Canada.</td>
<td>EU (incl UK), USA, and Australia.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
<td>Randomised, placebo-controlled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=92 (planned); aged ≥18 yrs; clinical diagnosis of acquired TTP requiring daily PEX; platelet count ≤100 x 10(^9)/L.</td>
<td>n=75; aged ≥18 yrs; clinical diagnosis of acquired TTP requiring daily PEX; platelet count ≤100 x 10(^9)/L.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to caplacizumab as an initial 10mg IV dose on day 1, then daily at 10mg SC injections for the duration of daily PEX and 30 days thereafter in addition to standard of care treatment; or placebo as an initial IV dose on day 1, then daily SC injections for the duration of PEX and 30 days thereafter in addition to standard of care treatment.</td>
<td>Randomised to caplacizumab as an initial 10mg IV on day 1, then daily or twice daily at 10mg SC injections for maximum treatment duration of 90 days; or placebo as an initial IV dose on day 1, then daily SC injections for maximum treatment duration of 90 days.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment for duration of daily PEX and 30 days thereafter, follow-up 28 days.</td>
<td>Active treatment for maximum 90 days, follow-up 12 mths.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Time to initial platelet count ≥150 x 10(^9)/L.</td>
<td>Reduction of time to recovery.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Recurrence of TTP, refractoriness to treatment, treatment-emergent major thromboembolic events, organ damage markers, mortality rate, adverse events.</td>
<td>Reduction of number of relapses, reduction of number of exacerbations.</td>
</tr>
<tr>
<td>Key results</td>
<td>-</td>
<td>Time to a response was significantly reduced with caplacizumab as compared with placebo (39% reduction in median time, p=0.005). Three patients in the caplacizumab group had an exacerbation, as compared with 11 patients in the</td>
</tr>
</tbody>
</table>
placebo group. Eight patients in the caplacizumab group had a relapse in the first month after stopping the study drug. Bleeding-related adverse events, most of which were mild to moderate in severity, were more common with caplacizumab than with placebo (54% vs. 38%).

Expected reporting date

Primary completion date reported as October 2017, reporting date is expected to be January 2018.

ESTIMATED COST and IMPACT

COST

The cost of caplacizumab is not yet known.

IMPACT - SPECULATIVE

Impact on Patients and Carers

☐ Reduced mortality/increased length of survival  ☛ Reduced symptoms or disability
☐ Other  ☐ No impact identified

Impact on Health and Social Care Services

☐ Increased use of existing services: additional injections.  ☛ Decreased use of existing services: regular SC injections have the potential for self-administrationb.
☐ 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  ☐ None identified

Other Issues

☑ Clinical uncertainty or other research question identified: routine use of caplacizumab in acute acquired TTP is not indicated as relatively modest reduction in the acute episode does not justify increased bleeding (albeit minor) or cost. It may however be useful in the following situations: acute idiopathic TTP in patients presenting with evidence of significant cardiac involvement (cardiac troponin I >0.25μg/l) – shown to have

b Expert personal opinion
a three fold risk of early mortality), management of refractory disease, and as a bridge to PEX – given with plasma infusion if there is unavoidable delay in starting PEX (e.g. delay in transfer to PEX centre). c

REFERENCES


c Expert personal opinion