

Health Technology Briefing January 2022

Danicopan with eculizumab or ravulizumab for treating paroxysmal nocturnal haemoglobinuria

Company/Developer

Alexion Pharmaceuticals Inc

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 30212

NICE ID:10752

UKPS ID: 660231

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Danicopan is in clinical development as an add-on therapy to eculizumab or ravulizumab for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH). PNH is a rare, long-term and life-threatening blood disease in which red blood cells (RBCs) are attacked by a group of proteins in the body's immune system, which are collectively known as complement proteins. This attack by complement proteins results in excessive breakdown of RBCs (haemolysis) and leads to a large amount of haemoglobin (the protein found in RBCs that carries oxygen around the body) being released into the urine. The condition is caused by a mutation (DNA change) that results in a lack of certain proteins being present on the surface of RBCs that normally protect them from being destroyed by complement proteins. Symptoms of PNH can include anaemia, breathlessness, difficulty swallowing, fatigue, blood clots and kidney damage. Some patients do not respond adequately to current treatment with eculizumab or ravulizumab alone, so there is a need to develop additional treatment options for PNH.

Danicopan is given to patients as an oral tablet and works by blocking the action of a complement protein called factor D. Blocking this protein is expected to help prevent complement proteins from damaging RBCs and thereby relieving symptoms of the disease. The addition of danicopan to eculizumab or ravulizumab is expected to result in improved outcomes compared to treatment with either eculizumab or ravulizumab alone. If licensed as an add-on therapy, danicopan may offer an additional treatment option for patients with PNH who have clinically evident extravascular haemolysis (EVH) despite current treatment with eculizumab or ravulizumab.

Proposed Indication

As an add-on therapy to complement component 5 (C5) inhibitor (either eculizumab or ravulizumab) in patients with PNH who have clinically evident extravascular haemolysis (EVH).¹

Technology

Description

Danicopan (ACH-0144471, ALXN2040) is a first-in-class, small molecule, orally administered complement factor D inhibitor that prevents new alternative pathway C3 convertase formation.^{1,2} Consequently, proximal inhibition at the level of factor D blocks alternative pathway-initiated upstream events and up to 80% of classical or lectin pathway-initiated downstream events via amplification-loop inhibition. Therapeutic factor D inhibition was developed to control intravascular haemolysis and prevent C3-mediated extravascular haemolysis. In vitro, danicopan has been shown to inhibit both alternative pathway mediated haemolysis and C3 fragment deposition on red blood cells (RBCs) from PNH patients.²

Danicopan is currently in clinical development as an add-on therapy to C5 inhibitor therapy (either eculizumab or ravulizumab), in adult patients with PNH who have clinically evident EVH. In the phase III clinical trial (ALPHA, NCT04469465, EudraCT 2019-003829-18), participants will receive 100-200mg danicopan, administered as an oral tablet, in addition to their usual dose and schedule C5 inhibitor therapy for 24 weeks.^{1,3}

Key Innovation

Treatment with C5 inhibitors eculizumab or ravulizumab, block terminal complement activation and subsequent intravascular haemolysis (which can be a major cause of morbidity and mortality) and have been shown to improve quality of life and survival for patients with PNH. However, some patients still experience residual anaemia after treatment, and around 15-20% of patients will also remain transfusion dependent.⁴ Danicopan blocks complement upstream of the C3 convertase. By targeting factor D inhibition with a small molecule, this represents an important treatment advancement for patients with PNH because proximal activator protein inhibition may disable both terminal complement activation (inhibiting MAC-mediated intravascular haemolysis) and C3 fragment opsonisation (preventing extravascular haemolysis), with additional convenience of oral administration.^{2,4}

Results from a phase II clinical study where PNH participants received oral danicopan in addition to their usual dose and schedule of eculizumab, reported a clinically meaningful reduction in RBC transfusion requirements during the study.^{4,5} If licenced, danicopan has the potential to be the first oral PNH therapy, and offers an opportunity to enhance the well-characterised efficacy of C5 inhibitors without compromising safety.⁶

Regulatory & Development Status

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

Danicopan has been awarded the following regulatory designations:

- PRIME designation by the EMA in November 2019 for the treatment of PNH patients who are not adequately responding to a C5 inhibitor.⁷
- Orphan drug status by the EMA in December 2017 for the treatment of PNH.⁸
- Breakthrough therapy designation by the FDA in September 2019 for the treatment of PNH patients who are sub-optimal responders to a C5 inhibitor alone.⁹
- Orphan drug designation by the FDA in November 2017 for the treatment of PNH.¹⁰

Danicopan is also in phase II development for geographic atrophy.¹¹

Patient Group

Disease Area and Clinical Need

PNH is rare, life-threatening disease of the blood. It is characterised by excessive breakdown of RBCs (haemolysis), leading to the release into the urine of a large amount of haemoglobin, a protein which is necessary to transport oxygen throughout the body.⁸ Chronic haemolysis is central to all the symptoms associated with PNH which include: fatigue, rapid heartbeat, headaches, chest pain, blood in the urine and difficulty breathing. In severe cases, additional symptoms can develop including: disabling fatigue, difficulty swallowing, oesophageal spasm, erectile dysfunction, blood clots or chronic kidney disease. PNH develops when PIG-A gene mutations occur in bone marrow stem cells. The affected stem cells pass on the PIG-A mutation to the mature blood elements (RBCs, white blood cells, and platelets) which are derived from bone marrow stem cells. Cells harbouring PIG-A mutations are deficient in a class of proteins called glycosyl phosphatidylinositol (GPI) anchored proteins. This makes RBCs in PNH patients extremely susceptible to destruction by the complement system, a complex group of proteins within the immune system that work together to fight infection.^{12,13} PNH is an acquired, not inherited, condition and having aplastic anaemia is the only known risk factor for developing PNH.^{14,15}

The incidence of PNH in Great Britain has been estimated to be 1 in 770,000 each year, with a predicted prevalence of approximately 1 in 62,500. It is estimated that there are around 650 to 900 people in England with PNH. The disease can occur at any age but is most frequently diagnosed between the ages of 30-40 years old.¹⁵ In England, 2020-21, there were 445 finished consultant episodes (FCEs) and 431 admissions for PNH [Marchiafava-Micheli] (ICD-10 code D59.5) which resulted in 390 day cases and 104 FCE bed days.¹⁶

Recommended Treatment Options

NICE currently recommends ravulizumab for treating PNH.¹⁷

Current clinical management for PNH patients can also include treatment with complement inhibitor eculizumab. Allogeneic stem cell transplantation may be curative but is associated with significant risks and is only considered for patients with severe bone marrow failure. Other interventions, notably RBC transfusion, folic acid, iron tablets and anti-coagulant treatments are offered to prevent or treat complications associated with PNH.¹⁵

Clinical Trial Information

Trial	<p>ALPHA, NCT04469465, EudraCT 2019-003829-18; A Phase 3 Study of Danicopan (ALXN2040) as Add-on Therapy to a C5 Inhibitor (Eculizumab or Ravulizumab) in Patients With Paroxysmal Nocturnal Haemoglobinuria Who Have Clinically Evident Extravascular Haemolysis</p> <p>Phase III – Recruiting</p> <p>Locations: 6 EU countries, UK, United States and other countries</p> <p>Primary completion date: October 2022</p>
Trial Design	Randomised, parallel assignment, double-blind, placebo controlled
Population	N=84; adults aged 18 years and older; clinically evident extravascular haemolysis; receiving a C5 inhibitor for at least 6 months prior to day 1; platelet count $\geq 30,000/\mu\text{L}$; absolute neutrophil count $\geq 750/\mu\text{L}$
Intervention(s)	Danicopan (oral tablet) in addition to participants usual dose and schedule of current C5 inhibitor therapy (either eculizumab or ravulizumab)
Comparator(s)	Placebo (oral tablet) in addition to participants usual dose and schedule of current C5 inhibitor therapy (either eculizumab or ravulizumab)
Outcome(s)	<p>Primary outcome: Change from baseline in haemoglobin [Time frame: Baseline to week 12]</p> <p>See trial record for full list of other outcome measures</p>
Results (efficacy)	-
Results (safety)	-

Trial	<p>NCT03472885, EudraCT 2016-003526-16; A Phase 2 Open-label Study of ACH-0144471 in Patients With Paroxysmal Nocturnal Haemoglobinuria Who Have an Inadequate Response to Eculizumab Monotherapy</p> <p>Phase II – Active, not recruiting</p> <p>Locations: UK, United States and Italy.</p> <p>Actual primary completion date: September 2019</p>
Trial Design	Non-randomised, sequential assignment, open-label
Population	N=12; adults aged 18 years to 65; diagnosed with PNH; received at least 1 blood cell transfusion within the last 12 weeks; anaemia with adequate reticulocytosis; currently on a stable regimen of eculizumab; platelet count $\geq 40,000/\mu\text{L}$
Intervention(s)	Danicopan (oral administration) in addition to participant's usual dose and schedule of eculizumab (intravenous administration)
Comparator(s)	No comparator
Outcome(s)	<p>Primary outcome: Change from baseline in haemoglobin [Time frame: Baseline to week 24]</p> <p>See trial record for full list of outcome measures.</p>
Results (efficacy)	Addition of danicopan resulted in a mean haemoglobin increase of 2.4g/dL at week 24 and reduced transfusion requirements in patients with PNH who were

	transfusion-dependent on eculizumab. In the 24 weeks prior to danicopan, 10 patients received 31 transfusions (50 units) compared with 1 transfusion (2 units) in 1 patient during the 24-week treatment period. Mean Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score increased by 11 points from baseline to week 24. ⁵
Results (safety)	The most common adverse events were headache, cough, and nasopharyngitis. ⁵

Estimated Cost

The estimated cost of danicopan is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria (GID-TA10651). Expected January 2022.
- NICE technology appraisal. Ravulizumab for treating paroxysmal nocturnal haemoglobinuria (TA698). May 2021.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Paroxysmal Nocturnal Haemoglobinuria Service (Adults and Adolescents). B05/S(HSS)/a.

Other Guidance

- PNH Education and Study Group (PESG). PESG PNH diagnosis, follow-up and treatment guidelines. 2016.¹⁸

Additional Information

References

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