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ALXN 1210 for paroxysmal nocturnal haemoglobinuria – first line

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LAY SUMMARY

Paroxysmal nocturnal haemoglobinuria (PNH) is an ultra-rare life-threatening blood disorder. Symptoms and signs of PNH are varied and can include: fatigue; dark red/brown urine; difficulty swallowing and abdominal pain and infections and bruising. PNH is a disorder with an age-at-onset typically ranging from the early thirties to the mid-forties, and often persisting for decades, with a continued dependence on blood transfusions in a proportion of patients.

ALXN1210 is an antibody under development that prevents the destruction of red blood cells (RBCs). The drug is administered by intravenous injection that requires fewer dosing regimen compared to current treatment option. If ALXN1210 is licensed for use in the UK, it could represent an additional treatment option for patients with paroxysmal nocturnal haemoglobinuria.

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TARGET GROUP

Paroxysmal nocturnal haemoglobinuria (PNH) – first line for patients consistent with the current English PNH National Service eligibility criteria for treatment with Soliris (eculizumab).[a]

TECHNOLOGY

DESCRIPTION

ALXN1210 is a monoclonal antibody that binds to terminal complement protein C5, a part of the complement system, thereby blocking C5 cleavage into pro-inflammatory components and preventing the complement-mediated destruction of red blood cells (RBCs) as seen in patients with PNH.[1]

In the phase III studies ongoing for ALXN1210 (NCT02946463 and NCT03056040) in patients with PNH adult patients with PNH in experimental arm received ALXN1210 in a weight-based dosing regimen as follows:

Single loading dose on Day 1, followed by regular maintenance dosing beginning on Day 15:

- ≥ 40 to <60 kg: 2400 mg loading, then 3000 mg every 8 weeks
- ≥ 60 to <100 kg: 2700 mg loading, then 3300 mg every 8 weeks
- ≥100 kg: 3000 mg loading, then 3600 mg every 8 weeks

ALXN1210 does not currently have Marketing Authorisation in the EU for any indication.

In addition to PNH, ALXN1210 is under investigation in Phase III trials for atypical haemolytic uremic syndrome (aHUS).[1]

INNOVATION and/or ADVANTAGES

Eculizumab, the current standard of care for PNH, is the first and only approved treatment for patients with PNH.[2] ALXN1210 was designed to have a longer serum half-life and corresponding duration of pharmacologic activity relative to eculizumab. Compared to eculizumab, which requires dosing every two weeks, ALXN1210 extends the dosing interval to 8 weeks and is expected to produce sustained terminal complement inhibition over this time period, reducing the potential risk of breakthrough complement-mediated haemolysis and improving the overall health of patients.

ALXN1210, if licenced, will offer an additional safe and effective treatment option for healthcare providers treating patients with PNH. It may potentially decrease the burden on health care resource utilization and a positively impact on quality of life of patients with PNH.

DEVELOPER

Alexion Pharmaceuticals

AVAILABILITY, LAUNCH or MARKETING

ALXN1210 was designated an orphan drug for PNH in the EU in June 2016 and in the US in January 2017.

[a] Information provided by company

PATIENT GROUP

BACKGROUND

PNH is an ultra-rare, progressively debilitating, life-threatening, genetic haematopoietic stem cell disease that manifests with haemolytic anaemia and thrombosis, as well as peripheral blood cytopenias due to impaired bone marrow function.[3,4] Patients with PNH are at an increased risk of thromboembolism, end-organ damage, poor quality of life and early mortality.

PNH occurs when mutations of a gene called PIG-A occur in a bone marrow stem cell. Stem cells give rise to red blood cells, white blood cells and platelets. In PNH, all cells that arise from the defective stem cell also carry the mutated PIG-A gene. These cells are deficient in a class of proteins called glycosylphosphatidylinositol (GPI) anchored proteins. Certain GPI-anchored proteins protect red blood cells from destruction while some are involved in blood clotting. The majority of PNH-related issues, including the haemolytic anaemia and thrombosis result from a deficiency in these proteins.[3]

Complement activation in PNH is manifested as chronic haemolysis that leads to the release of free haemoglobin and the subsequent depletion of nitric oxide. Consumption of nitric oxide leads to vaso-occlusion and platelet activation and results in the common morbidities seen in PNH, such as fatigue, dyspnoea, recurrent abdominal pain, dysphagia, chest pain and pulmonary hypertension. More importantly, chronic haemolysis renders PNH patients at a greater risk of thrombotic events (TEs), renal insufficiency and other organ damage, and premature mortality. Compared with the general population, patients with PNH have a 62-fold higher risk of a TE[5] and a six-fold greater risk of chronic kidney disease (CKD).[6] TEs have been reported to account for up to 67% of PNH-related deaths,[7] while CKD has been reported to account for 8–18% of disease-related mortality.[8,9]

Patients with PNH suffer from the direct effects of intravascular haemolysis that result in the absorption of nitric oxide, a key molecule in homeostasis, leading to smooth muscle dysfunction, platelet activation and other consequences. This often results in severe disabling abdominal pain, dysphagia, and profound lethargy and, in men, erectile dysfunction. Intravascular haemolysis can also contribute to many of the complications seen in PNH such as thromboses, renal impairment and raised pulmonary pressures.[10]

Approximately half of patients with PNH die as a direct result of their disease, many others are transfusion-dependent for decades and, for most patients with haemolytic PNH, the disease has a major impact on quality of life. Pregnancy is extremely high risk in PNH, with reported maternal mortalities of up to 20%, predominantly resulting from thrombotic complications, and reports of a high incidence of foetal loss.[10]

CLINICAL NEED and BURDEN OF DISEASE

A single study conducted in the UK reported the 15-year prevalence of PNH to be 1.59/100,000 in 2007.[11] At the time of this briefing, no further studies have been identified that assessed the incidence and prevalence of this condition in the UK population.

There are currently over 2,500 patients with PNH from 28 countries have been included in the Registry and referred to the English National PNH Service.[12] In the UK, there are currently over 500 patients with PNH that have been investigated and referred to the PNH Service.[13] The UK is the second largest recruiting country having entered over 350 patients.[12]

The burden of disease in PNH is significant. According to Weitz I, et al.,[14] and Schrezenmeier H, et al.,[15]**:**

- 97% of patients report fatigue independent of anaemia/transfusion requirements
- 76% of patients with PNH have disruptions in daily activities
- 17% of patients were unemployed due to PNH
- 66% of patients report shortness of breath
- 59% of patients report abdominal pain

The Hospital Episodes Statistics for England 2016/2017 recorded 585 finished consultant episodes (FCE), 569 hospital admissions and 187 FCE beds due to PNH (ICD-10 code D59.5).[16]

PATIENT PATHWAY

There is an English National PNH Service. The Service aims to review and manage all patients with PNH through a shared care agreement with their own local haematology units. The Service reviews and monitors not only patients requiring eculizumab but also all other patients with PNH for potential changes and complications. To ensure that all patients with PNH have equal access to effective therapy, in particular eculizumab, there is agreed criteria for selecting patients who would benefit from this treatment. This facilitates cost-effective and auditable use.[b]

RELEVANT GUIDANCE

NICE GUIDANCE

None identified

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Paroxysmal Nocturnal Haemoglobinuria Service Adults and Adolescents. B05/S(HSS)/a.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.

OTHER GUIDANCE

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- Sutherland DR, Keeney M and Illingworth A. Practical guidelines for the high-sensitivity detection and monitoring of paroxysmal nocturnal hemoglobinuria clones by flow cytometry. *Cytometry* Part B 2012; 82B: 195–208.[19]

CURRENT TREATMENT OPTIONS

[b] Information provided by company

Prior to the availability of eculizumab, there were no approved therapies for the treatment of patients with PNH. Treatment for PNH involved blood transfusions, folic acid, anticoagulants, iron supplements or iron removal. Historically, two treatment approaches were available for patients with PNH:[20]

1. Symptomatic treatment and prophylaxis of complications.
2. Stem cell transplantation (SCT).

Symptomatic treatment such as red blood cell transfusions, supplementation with folic acid, vitamin B12 (if deficient), iron replacement (based on iron stores), prevention/early treatment of bacterial infections, prophylactic or post-thrombotic anticoagulation, corticosteroids and or immunosuppressive treatment (in patients with aplastic anaemia-PNH syndrome/relevant bone marrow hypofunction) give unsatisfactory long-term disease control.

Importantly, these supportive care approaches do not address the complement-mediated intravascular haemolysis that is the underlying cause of progressive, severe and life-threatening morbidities and early mortality in PNH. In addition, there are no controlled trials indicating that supportive care measures are effective or safe in patients with PNH with regard to patient outcomes.[21]

SCT has the potential to cure patients with PNH, but also has high treatment-related morbidity and mortality due to infections, Graft-versus-host disease (GVHD), and graft failure.

EFFICACY and SAFETY

Trial	NCT03056040 18 years and older; phase III
Sponsor	Alexion Pharmaceuticals
Status	Ongoing
Source of Information	Global Data,[22] Trial registry[23]
Location	United States, Australia, Canada , France, Germany, Italy, Japan, Netherlands ,South Korea, United Kingdom
Design	Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab
Participants	197
Schedule	2 arms: Experimental: 1210 Biological/Vaccine: ALXN1210 Single loading dose on Day 1, followed by regular maintenance dosing beginning on Day 15, based on weight. • ≥ 40 to <60 kg: 2400 mg loading, then 3000 mg every 8 weeks • ≥ 60 to <100 kg: 2700 mg loading, then 3300 mg every 8 weeks • ≥100 kg: 3000 mg loading, then 3600 mg every 8 weeks Active: Eculizumab Regular maintenance dosing beginning on Day 1, then every 2 weeks to Day 183. Single loading dose of ALXN1210 on Day 183, followed by regular maintenance dosing beginning on Day 197, based on weight. • ≥ 40 to <60 kg: 2400 mg loading, then 3000 mg every 8 weeks • ≥ 60 to <100 kg: 2700 mg loading, then 3300 mg every 8 weeks • ≥100 kg: 3000 mg loading, then 3600 mg every 8 weeks
Follow-up	2 years

Primary Outcomes	Primary Outcome Measure: • Haemolysis as directly measured by percentage change in LDH levels [Time Frame: 26 weeks] The difference between treatment arms in LDH-PCHG from Baseline to Day 183
Secondary Outcomes	Secondary Outcome Measures: • Change from baseline in quality of life as assessed by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue [Time Frame: 26 weeks] Change in quality of life as assessed by the FACIT-Fatigue scale will be compared between the treatment groups from Baseline to Day 183 • Percentage of patients who achieve Transfusion Avoidance (TA) [Time Frame: 26 weeks] The proportion of patients who remain transfusion-free will be compared between treatment groups from Baseline to Day 183 • Percentage of patients with stabilized hemoglobin [Time Frame: 26 weeks] The percentage of patients with stabilized hemoglobin will be compared between the treatment groups from Baseline to Day 183.
Key Results	Not available
Adverse effects (AEs)	Not available
Expected reporting date	Not available

Trial	NCT02946463 18 years and older; phase III
Sponsor	Alexion Pharmaceuticals
Status	Ongoing
Source of Information	Global data,[24] trial registry[25]
Location	USA, Argentina, Australia, Austria, Belgium, Brazil, Canada, Colombia, Czechia, Estonia, France, Germany, Italy, Japan, Malaysia, Mexico, Poland, Russia, Singapore, South Korea, Spain, Sweden, Taiwan, Thailand, Turkey, United Kingdom
Design	A Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Complement Inhibitor-Naïve Adult Patients With Paroxysmal Nocturnal Haemoglobinuria
Participants	246
Schedule	Experimental 1210 Single loading dose on Day 1, followed by regular maintenance dosing beginning on Day 15, based on weight. • ≥ 40 to <60 kg: 2400 mg loading, then 3000 mg every 8 weeks • ≥ 60 to <100 kg: 2700 mg loading, then 3300 mg every 8 weeks • ≥100 kg: 3000 mg loading, then 3600 mg every 8 weeks Active Comparator: Eculizumab Induction doses of 600 mg on Days 1, 8, 15, and 22, followed by regular maintenance dosing of 900 mg beginning on Day 29 and every 2 weeks thereafter
Follow-up	2 years

Primary Outcomes	Primary Outcome Measure: • Normalization of lactate dehydrogenase (LDH) levels [Time Frame: 26 weeks] Achievement of LDH values within the laboratory normal range will be compared between treatment groups. LDH is an indicator of intravascular haemolysis that occurs in patients with paroxysmal nocturnal haemoglobinuria (PNH). A decrease in LDH from above the upper limit of normal (ULN) to below the ULN indicates reduction (improvement) in haemolysis. • Percentage of patients who achieve transfusion avoidance (TA) [Time Frame: 26 weeks]
Secondary Outcomes	Percentage change from baseline in lactate dehydrogenase (LDH) levels [Time Frame: 26 weeks] • Change from baseline in quality of life as assessed by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue [Time Frame: 26 weeks] • Percentage of patients with stabilized haemoglobin [Time Frame: 26 weeks
Key Results	Not available
Adverse effects (AEs)	Not available
Expected reporting date	Not available

ESTIMATED COST and IMPACT

COST

The cost of ALXN-1210 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

☒ Decreased use of existing services: treatment with ALXN is given every 8 weeks (instead of every 2 weeks) reducing use of existing services

☐ 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: ☒ None identified

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