

HEALTH TECHNOLOGY BRIEFING DECEMBER 2019

Pegcetacoplan (APL-2) for paroxysmal nocturnal haemoglobinuria

NIHRIO ID	15018	NICE ID	10076
Developer/Company	Apellis Pharmaceuticals Inc.	UKPS ID	Not available

Licensing and market availability plans

Currently in Phase III trials.

*COMMERCIAL IN CONFIDENCE

SUMMARY

Pegcetacoplan (APL-2) is a medicinal product in clinical development for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH). PNH is an ultra - rare life - threatening blood disorder. PNH leads to excessive breakdown of red blood cells, leading to the release of a large amount of haemoglobin (the protein found in red blood cells that carries oxygen around the body) into the urine. Symptoms and signs of PNH are varied and can include: fatigue; dark red/brown urine; difficulty swallowing, abdominal pain, infections, and bruising. PNH typically starts 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.

Pegcetacoplan targets and inhibits the activation of an important protein in the complement system called C3 that plays a key role in PNH. By inhibiting C3 activation, the medicine is expected to block the chain of reactions that damage the red blood cells, thus relieving the symptoms of the disease. Pegcetacoplan is given by subcutaneous injection for self-administration. If licensed, Pegcetacoplan could represent an additional treatment option for patients with PNH.

PROPOSED INDICATION

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

Pegcetacoplan is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH)

TECHNOLOGY

DESCRIPTION

Pegcetacoplan (APL-2) is a PEGylated cyclic peptide inhibitor of complement C3. PEGylation helps keep APL-2 in the body longer, reducing dosing frequency. The peptide portion of APL-2 binds to C3, exerting broad inhibition of the complement cascade and helping to restore normal complement activity.¹

Pegcetacoplan is a potential therapeutic option for various diseases in which uncontrolled or excessive complement activation plays a key role, including paroxysmal nocturnal haemoglobinuria (PNH). Upon administration, pegcetacoplan selectively binds to C3 and blocks the cleavage of C3 into C3a and C3b by C3 convertase. C3b also participates to the formation of the C5 convertase that cleaves downstream C5 into C5a and C5b. Therefore, pegcetacoplan inhibits broadly complement-mediated inflammation and cell destruction.²

Pegcetacoplan is in clinical development for the treatment of patients with PNH. In the phase III extension clinical trial (NCT03531255), 1,080mg pegcetacoplan will be administered subcutaneously twice weekly or every three days.³

INNOVATION AND/OR ADVANTAGES

Pegcetacoplan has been designed to target complement proteins centrally at the level of C3, thus introducing a separate class of treatment. It is believed that this approach can result in broad inhibition of the complement pathways and has the potential to effectively control complement-dependent diseases, including PNH. It is indicated that previously reported interim data from phase Ib trials showed improvements in lactate dehydrogenase and haemoglobin levels in patients who are suboptimal responders to eculizumab and untreated patients, respectively.⁴ It is believed that pegcetacoplan may address the limitations of existing treatment options or provide a treatment option where there is none.⁵

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pegcetacoplan is not currently licensed for any indication in the EU/UK.

Pegcetacoplan is in phase III development for geographic atrophy.⁶

Pegcetacoplan is in phase II development for:⁶

- Glomerulopathies
- Warm autoimmune haemolytic anaemia and cold agglutinin disease
- Neovascular age related macular degeneration

Pegcetacoplan was granted Orphan Drug designation in the EU in May 2017 for the treatment of PNH.⁷

DISEASE BACKGROUND

Paroxysmal nocturnal haemoglobinuria (PNH) is a condition in which there is excessive breakdown of red blood cells (haemolysis), leading to the release of a large amount of haemoglobin into the urine (the protein found in red blood cells that carries oxygen around the body).⁷

PNH occurs when mutations of a gene called phosphatidylinositol N-acetylglucosaminyltransferase subunit A (PIG-A) occur in a bone marrow stem cell. Stem cells give rise to all the mature blood elements including red blood cells, which carry oxygen to the tissues; white blood cells, which fight infection; and platelets, which are involved in forming blood clots. In PNH, the affected stem cell passes the PIG-A mutation to all cells derived from the abnormal stem cell. Cells harbouring PIG-A mutations are deficient in a class of proteins called glycosylphosphatidylinositol (GPI)-anchored proteins. Certain GPI-anchored proteins protect red blood cells from destruction, some are involved in blood clotting, and others are involved in fighting infection.⁸

The absence of GPI- anchored proteins on PNH erythrocytes renders them susceptible to terminal complement-mediated haemolysis. Haemolysis most likely contributes to thromboembolism (TE) in PNH. TE is the leading cause of mortality in patients with PNH, and an initial thrombotic event increases the relative risk of death in PNH 5- to 10-fold.⁹ The most common complication of PNH is venous or arterial thrombosis. Thrombosis occurs in approximately half of patients with haemolytic PNH and is the cause of death in a third of patients. Approximately 10% of patients present with thrombosis as the first manifestation of their PNH.¹⁰

There can be a marked variation in the signs and symptoms observed due to PNH both between patients and in the same patient at different times. Common symptoms include haemoglobinuria, anaemia, breathlessness, difficulty swallowing and abdominal pain, erectile dysfunction, fatigue, jaundice, kidney damage and blood clots.¹¹

Renal failure is extremely common in PNH and has been reported to contribute to between 8% and 18% of the deaths due to the disease. PNH often affects young adults (although it is seen in all ages) which usually persists for the remainder of the patient's life and results in the death of approximately half of sufferers.¹⁰

CLINICAL NEED AND BURDEN OF DISEASE

Although PNH has been described worldwide, exact prevalence data are not available.¹² In 2017, PNH affected less than 0.1 in 10,000 people in the European Union (EU).⁷ An incidence estimate of about 1 per 770,000 per year has been reported with a predicted prevalence of approximately 1 per 62,500 in Great Britain.¹² Using the 2017-2018 population estimates, there are 1027 people with PNH in Great Britain.¹³

According to the Highly Specialised Services Highlight Report 2016/17 by NHS England, about 650 people in England suffer from PNH.¹⁴

According to HES data for England, in 2017-2018 there were 531 admissions which resulted in 471 day cases and 203 FCE bed days due to PNH (ICD-10 code: D59.5).¹⁵

PNH can occur at any age but is most frequently diagnosed between the ages of 30-40 years old. Ten-year survival has been estimated to range between 65% and 76%.¹⁶

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The PNH Education and Study group (PESG) report that PNH treatment can be grouped under three headings:¹⁷

- Supportive treatments and immunosuppressive treatments
- Treatment changing the course of the disease
- Potential curative treatment

Currently, allogeneic bone marrow transplantation is the only potential curative treatment option for PNH.

CURRENT TREATMENT OPTIONS

According to the PESG, supportive treatments and immunosuppressive treatments include:¹⁷

- Blood/erythrocyte suspension transfusion
- Oral iron supplementation
- Steroids
- Anticoagulant treatment
- Immunosuppressive treatment

Treatment changing the course of the disease include:

- Eculizumab
- Meningococcal prophylaxis

Potential curative treatment:

- Allogeneic bone marrow transplantation

PLACE OF TECHNOLOGY

If licensed, pegcetacoplan will offer a new treatment option for patients with PNH.

CLINICAL TRIAL INFORMATION

Trial	NCT03500549 , APL2-302; APL-2 vs Eculizumab; phase III
Sponsor	Apellis Pharmaceuticals, Inc.
Status	Ongoing
Source of Information	Trial registry ¹⁸
Location	USA, Canada, Australia, Japan, Republic of Korea, Europe (incl. UK)
Design	Randomised, multi-centre, open-label, active-comparator controlled
Participants	N=70 (planned); aged 18 years and older; primary diagnosis of PNH confirmed by high-sensitivity flow cytometry; on treatment with eculizumab (dose must have been stable for at least 3 months prior to screening); Hb <10.5 g/dL; Absolute reticulocyte count >1.0x ULN; Platelet count of >50,000/mm ³ ; Absolute neutrophil count >500/mm ³

Schedule	Randomised to APL-2, administered subcutaneously twice weekly or every 3 days
Follow-up	Not reported.
Primary Outcomes	Hemoglobin [Time Frame: 16 weeks] - Week 16 change in baseline in haemoglobin level
Secondary Outcomes	<ul style="list-style-type: none"> • APL-2 plasma concentrations (and PK parameters as appropriate) • Change from baseline in FACIT Fatigue Scale score • Change from baseline in reticulocyte count • Change from baseline in total bilirubin • Number of RBC transfusions per month • Change from baseline in Linear Analog Scale Assessment (LASA) for Quality of Life
Key Results	Expected January 2020.
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as December 2019. Estimated study completion date reported as October 2020.

Trial	NCT03531255 , APL2-307; APL-2; phase III extension
Sponsor	Apellis Pharmaceuticals, Inc.
Status	Ongoing
Source of Information	Trial registry ³
Location	USA, Canada, Australia, Japan, Republic of Korea, Malaysia, Thailand, Europe (incl. UK)
Design	Non-randomised, multi-centre, open label, extension
Participants	N=109 (planned); aged 18 years and older; subjects with PNH who have participated in an APL-2 clinical trial and have experienced clinical benefit in the opinion of the Investigator.
Schedule	Randomised to 1,080mg APL-2 administered subcutaneously twice weekly or every 3 days
Follow-up	Not reported.
Primary Outcomes	Incidence and severity of hematologic treatment-emergent adverse events [Time Frame: 48 weeks]
Secondary Outcomes	Mean change from baseline to 48 weeks in haemoglobin levels (g/dL) [Time Frame: 48 weeks]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as December 2020. Estimated study completion date reported as December 2020.

Trial	NCT04085601 , APL2-308; APL-2 vs Standard of Care (SOC) excluding complement inhibitors; phase III
Sponsor	Apellis Pharmaceuticals, Inc.

Status	Ongoing
Source of Information	Trial registry ¹⁹
Location	Malaysia, Poland
Design	Randomised, multicentre, open-label, controlled
Participants	N=54 (planned); aged 18 years and older; LDH ≥ 1.5 x ULN at the screening visit; PNH diagnosis, confirmed by high sensitivity flow cytometry; Hb less than LLN; Ferritin greater than/equal to the LLN, or total iron binding capacity less than/equal to ULN; Body mass index (BMI) < 35 kg/m ² at screening; platelet count of >50,000/mm ³ ; absolute neutrophil count >500/mm ³
Schedule	Randomised to 1,080mg APL-2 administered subcutaneously twice weekly
Follow-up	Not reported.
Primary Outcomes	Time frame: baseline through week 26: <ul style="list-style-type: none"> - Hemoglobin stabilisation defined as avoidance of a > 1g/dl decrease in haemoglobin levels in the absence of transfusion - Reduction in lactate dehydrogenase (LDH) level
Secondary Outcomes	<ul style="list-style-type: none"> - To evaluate the efficacy of APL-2, compared with standard of care (excluding complement inhibitors) - To evaluate the safety of APL-2
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as June 2020. Estimated study completion date reported as 30 September 2020.

Trial	NCT03593200 , APL2-202; APL-2; phase IIa
Sponsor	Apellis Pharmaceuticals, Inc.
Status	Ongoing
Source of Information	Trial registry ²⁰
Location	Bulgaria, Serbia
Design	Single arm, open label, multiple dose
Participants	N=4; aged 18 years and older; diagnosed with PNH (white blood cell (WBC) clone >10%); lactate dehydrogenase (LD) ≥ 2 times the upper limit of normal; screening Ferritin \geq normal and Total Iron Binding Capacity (TIBC) < LLN based on central lab reference ranges; last transfusion within 12 months of screening; platelet count of >30,000/mm ³ ; absolute neutrophil count >500/mm ³
Schedule	Participants received 270mg/day (up to 360 mg/day from day 29) from day 1 to day 364
Follow-up	Not reported.
Primary Outcomes	<ul style="list-style-type: none"> - Number of treatment emergent adverse events (TEAEs) following administration of multiple doses of SC APL-2. [Time Frame: Change from baseline up to week 36]. Severity of TEAEs following administration of multiple doses of SC APL-2. [Time Frame: Change from baseline up to week 36] - LDH (U/L) [Time Frame: Change from baseline up to week 32]

	- Haptoglobin (mg/dL) & Hemoglobin (g/dl) [Time Frame: Change from baseline up to Week 32]
Secondary Outcomes	Not reported.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as December 2019. Estimated study completion date reported as December 2019.

ESTIMATED COST

The cost of pegcetacoplan is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE highly specialised technologies guidance. Ravulizumab for treating paroxysmal nocturnal haemoglobinuria (GID-HST10023). Expected publication date: TBC.

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. Peg PNH diagnosis, follow-up and treatment guidelines. 2016.¹⁷

ADDITIONAL INFORMATION

Apellis Pharmaceuticals, Inc. 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.

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