Health Technology Briefing
August 2022

Iptacopan for paroxysmal nocturnal haemoglobinuria

Company/Developer	Novartis Pharmaceuticals UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27444	NICE ID: 10437	UKPS ID: 660898

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Iptacopan is in development for the treatment of paroxysmal nocturnal haemoglobinuria (PNH). PNH is a rare condition, which occurs due to a genetic change within cells in the bone marrow. In PNH, blood cells lack specific proteins on their surface which normally protect them from being destroyed (a process called haemolysis in red blood cells) by the body's normal defence system. PNH is characterised by the presence of brownish urine. The characteristic colour of urine is due to the presence of products from destroyed red blood cells. Patients have a low count of red blood cells and may have blood clots in the large vessels. The exact cause of PNH is not fully understood but it is known that the genetic mutation is acquired. PNH can be potentially life threatening, and thrombosis (blood clot) is recognised as the leading cause of death in PNH patients. There are currently few treatment options available for PNH and current treatments can be expensive.

Iptacopan is a small molecule inhibitor of a protein that acts within the immune pathway. By inhibiting this pathway, it reduces the dysregulation resulting in reduced cell destruction and associated complications. Currently inhibitors of this type lack specificity. If licenced, iptacopan will offer a novel treatment option for patients with PNH.

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.
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Proposed Indication

Treatment of paroxysmal nocturnal haemoglobinuria (PNH) in adult patients.[1-3]

Technology

Description

Iptacopan (LNP023) is an orally bioavailable, small-molecule inhibitor of complement factor B (FB) with potential immunomodulatory activity. It binds to FB within the body and prevents the formation of the alternative pathway (AP) C3- convertase, C3bBb. This limits the cleavage of C3 to the active fragment C3b and may prevent C3b-mediated extravascular haemolysis as a result.[4] It acts upstream of the C5 terminal pathway, preventing not only intravascular but also extravascular haemolysis in PNH. In doing so, iptacopan may have a therapeutic advantage over current first-line standard-of-care by targeting a key part of the biology responsible for PNH.[5-7]

Iptacopan is currently in clinical development for PNH in adults. In the phase III trials (NCT04558918, NCT04747613, NCT04820530), 200mg iptacopan is administered orally twice a day.[1-3]

Key Innovation

Currently known inhibitors of FB lack specificity and there are no FB inhibitors commercially available for therapeutic application. If approved, iptacopan would represent the first available FB inhibitor for patients with PNH.[6] First-line standard of care with anti-C5 treatment in PNH is generally effective, but some patients may have incomplete haematological responses to anti-C5 inhibitors and experience residual anaemia associated with breakthrough haemolysis (BTH) or C3-emerging extravascular haemolysis.[6,8-10] Therefore, iptacopan may be used as an alternative treatment option for treatment-naïve patients or in patients who are unstable on available treatment options.[11,12]

If licenced, iptacopan would offer a novel treatment option for adult patients with PNH.

Regulatory & Development Status

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

Iptacopan is in phase III/II clinical trials for:[13]

- Idiopathic membranous nephropathy
- C3 glomerulopathy
- IgA nephropathy
- Atypical hemolytic uremic syndrome

Iptacopan was awarded the following designations for the treatment of PNH:[14-16]

- Orphan drug status by the EMA in June 2020
- FDA Breakthrough Therapy Designation in December 2020
- FDA orphan drug status in July 2020

Patient Group

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Disease Area and Clinical Need

PNH is a rare condition that manifests with haemolytic anaemia, thrombosis, and peripheral blood cytopenias due to bone marrow failure.[17] PNH occurs due to a mutation in a gene called PIG-A within stem cells in the bone marrow. These stem cells give rise to red blood cells, white blood cells and platelets, therefore, when the PIG-A mutation occurs all cells derived from the affected stem cell carry the mutation. Mutated blood cells are deficient in a class of proteins called GPI-anchored proteins. Some of these proteins protect red blood cells from destruction and many clinical PNH manifestations result from a deficiency in GPI-anchored proteins.[18] The exact cause of PNH is not fully understood, but it is known that the PIG-A mutation is acquired and not present from birth.[19] It can occur at any age, but is usually diagnosed in young adulthood.[20] Symptoms of PNH can show a large amount of variation. Some people exhibit no symptoms, yet others may be affected by a number of different symptoms and complications. Common symptoms include; haemoglobinuria (dark or black urine due to haemoglobin in the urine), anaemia, breathlessness, difficulty swallowing, abdominal pain, erectile dysfunction in men, fatigue, jaundice, kidney damage and blood clots.[21] PNH can be potentially life-threatening and thrombosis is recognised as the leading cause of death in PNH patients.[22]

The incidence of PNH in Great Britain has been estimated as approximately 1 in 770,000 each year, with a predicted prevalence of approximately 1 in 62,500.[23] It is estimated that there are about 650 to 900 people in England with PNH.[23,24] In England (2020/21), there were 431 hospital admissions with primary diagnosis of PNH (ICD-10 code: D59.5), and 445 finished consultant episodes (FCEs), resulting in 104 FCE bed days and 390 day cases.[25]

Recommended Treatment Options

For treating PNH in adults, the National Institute for Health and Care Excellence (NICE) currently recommends the following treatment options:[26,27]

- Ravulizumab
- Pegcetacoplan (second-line)

Eculizumab was approved in 2007 by the European Medicines Agency (EMA) for the treatment of PNH in adults and children.[28] Eculizumab is recommended for reducing haemolysis in PNH patients with a history of blood transfusions (under expert supervision) and is commissioned by NHS England for the treatment of PNH in adults and adolescents as a highly specialised service.[29,30]

Clinical Trial Information

Trial	**APPLY-PNH, NCT04558918, 2019-004665-40;** A Randomised, Multicenter, Active-comparator Controlled, Open-label Trial to Evaluate Efficacy and Safety of Oral, Twice Daily LNP023 in Adult Patients With PNH and Residual Anaemia, Despite Treatment With an Intravenous Anti-C5 Antibody **Phase III –** active, not recruiting **Location(s):** 6 EU countries, UK, US and other countries **Primary Completion Date:** September 2022
Trial Design	Randomised, parallel assignment, open-label, active comparator
Population	N=97 aged 18 years and older; stable regimen of anti-C5 antibody treatment
Intervention(s)	200mg iptacopan orally twice a day

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Comparator(s)	• Eculizumab by intravenous infusion (IV) every two weeks, fixed dose • Ravulizumab by IV every 8 weeks, weight based dose
Outcome(s)	Primary outcome measures: • Percentage of participants achieving a sustained increase in haemoglobin levels of ≥ 2 g/dL in the absence of red blood cell transfusions • Percentage of participants achieving sustained haemoglobin levels ≥ 12 g/dL in the absence of red blood cell transfusions See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**APPOINT-PNH,** NCT04820530, 2020-003172-41; A Multicenter, Single-arm, Open-label Trial to Evaluate Efficacy and Safety of Oral, Twice Daily Iptacopan in Adult PNH Patients Who Are Naive to Complement Inhibitor Therapy **Phase III –** recruiting **Location(s):** 4 EU countries, UK and other countries **Primary Completion Date:** January 2023
Trial Design	Single group assignment, open-label
Population	N=40 (estimated); aged 18 years and older; a diagnosis of PNH confirmed by high-sensitivity flow cytometry
Intervention(s)	200mg iptacopan orally twice a day
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: • Proportion of participants achieving a sustained increase in haemoglobin levels of ≥ 2 g/dL in the absence of red blood cell transfusion See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT04747613; An Open Label, Multicenter Roll-over Extension Program (REP) to Characterize the Long-term Safety and Tolerability of Iptacopan (LNP023) in Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH) Who Have Completed PNH Phase 2 and Phase3 Studies With Iptacopan **Phase III –** recruiting **Location(s):** 7 EU countries, Japan, Malaysia, Taiwan and Republic of Korea. **Primary Completion Date:** May 2026
Trial Design	Single group assignment, open label
Population	N=167 (estimated); aged 18 years and older; had previous enrolment in prior studies

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Intervention(s)	200mg iptacopan orally twice daily
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: • Proportion of participants with adverse events See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT03439839; An Open Label, Single Arm, Multiple Dose Study to Assess Efficacy, Safety, Pharmacokinetics and Pharmacodynamics of LNP023 When Administered in Addition to Standard of Care (SoC) in Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH) With Signs of Active Haemolysis **Phase II** - Completed **Location(s):** 3 EU countries **Study Competition Date:** February 2022
Trial Design	Non-randomised, parallel assignment, open label
Population	N=16; aged 18 years and older; baseline diagnosis of PNH
Intervention(s)	• High dose iptacopan • Low dose iptacopan
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: • Reduction of chronic haemolysis See trial record for full list of outcomes.
Results (efficacy)	• Iptacopan resulted in marked reduction of lactate dehydrogenase from baseline versus at week 13 (mean 539 IU/L [SD 263] vs 235 IU/L [44], change from baseline −309·2 IU/L [SD 265·5], 90% CI −473·77 to −144·68, p=0·0081), associated with significant improvement of haemoglobin concentrations (mean 97·7 g/L [SD 10·5] vs 129·5 g/L [18·3] change from baseline 31·9 g/L [14·5], 90% CI 23·42–40·28, p<0·0001). • All biomarkers of haemolysis improved on iptacopan treatment. • Observed haematological benefits were maintained longer than the 13-week study period, throughout the study extension, including seven patients who stopped concomitant standard-of-care treatment and continued iptacopan as monotherapy.[12]
Results (safety)	• There were no deaths or treatment-related serious adverse events during the study period. • Of three non-related serious adverse events, two occurred in the same patient (one during run-in and before exposure to iptacopan).[12]

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Clinical Trial Information

Trial	NCT03896152; A Multi-center, Randomized, Open-label, Efficacy, Safety, Pharmacokinetics and Pharmacodynamics Study, Assessing Multiple LNP023 Doses in Adult Patients With Paroxysmal Nocturnal Hemoglobinuria and Active Haemolysis **Phase II** - Completed **Location(s):** Taiwan, Republic of Korea, Malaysia and Singapore **Study Completion Date:** February 2022
Trial Design	Randomised, parallel assignments, open label
Population	N=13; aged 18 years and older; diagnosis of PNH
Intervention(s)	• Low dose iptacopan orally, twice daily (25mg for 4 weeks followed by 100mg up to 2 years) • High dose iptacopan orally, twice daily (50mg for 4 weeks followed by 200mg up to 2 years)[31]
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: • Percentage of patients with reduction of Paroxysmal nocturnal haemoglobinuria (PNH) associated haemolysis See trial record for full list of outcomes.
Results (efficacy)	• At the time of interim analysis, of 13 PNH patients enrolled, all 12 evaluable for efficacy achieved the primary endpoint of reduction in serum lactate dehydrogenase (LDH) levels by at least 60% by week 12 as compared to baseline; mean LDH levels dropped rapidly and durably, namely by 77% and 85% at week 2 and by 86% and 86% at week 12 in cohorts 1 and 2, respectively. • Most patients achieved a clinically meaningful improvement in haemoglobin levels and all but one patient remained transfusion-free up to week 12. Other markers of haemolysis, including bilirubin, reticulocytes and haptoglobin, showed consistent improvements.[31]
Results (safety)	No thromboembolic events were reported, and iptacopan was well tolerated, with no severe or serious adverse events reported up until the data cut off.[31]

Estimated Cost

The cost of iptacopan is not yet known.

Relevant Guidance

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NICE Guidance

- NICE technology appraisal in development. Crovalimab for treating paroxysmal nocturnal haemoglobinuria. (GID-TA11062). Expected date of publication to be confirmed.
- NICE technology appraisal. Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria. (TA778). March 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 PNH diagnosis, follow-up and treatment guidelines. 2016.[32]

Additional Information

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