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Newcastle University

Health Technology Briefing
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Pegcetacoplan for treating C3 glomerulopathy or immune-complex membranoproliferative glomerulonephritis

Company/Developer	Swedish Orphan Biovitrum AB

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 24302	NICE ID: Not available	UKPS ID: 674017

Licensing and Market Availability Plans

Currently in phase II/III clinical trials.

Summary

Pegcetacoplan is in clinical development for treating C3 glomerulopathy (C3G) and primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN). C3G and primary IC-MPGN are both subtypes of membranoproliferative glomerulonephritis (MPGN). They result from an immune system disorder that causes antibodies and a substance called complement (C3) to be deposited in the kidneys, with evidence of immune complex deposition in the case of primary IC-MPGN, leading to inflammation that contributes to progressive renal injury. There is to date no specific treatment of C3G and primary IC-MPGN which directly targets C3 complement protein - the initial driver of the disease and possibly immunoglobulins deposition. There is a need for targeted therapies to improve the prognosis of both conditions.

Pegcetacoplan is a targeted C3 inhibitor that attaches to the C3 complement protein to prevent C3 activation and the formation of the membrane attack complex associated with renal impairment. It is intended to be administered under the skin in a 20 ml (1080 mg) infusion, twice weekly for adults and adolescents weighing greater than 50 kg. If licensed, pegcetacoplan will offer an additional treatment option for C3G and primary IC-MPGN who currently have few effective therapies available.

Proposed Indication

Patients aged 12 years or older with a diagnosis of primary C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN) with or without previous renal transplant.[1]

Technology

Description

Pegcetacoplan (Aspaveli, APL-2) is a targeted C3 and C3b inhibitor consisting of two 15-amino acid cyclic peptides conjugated to a linear polyethylene glycol moelcule to increase its half-life, that targets and attach to the C3 complement protein and its fragment C3b, which are part of the body's defence system called the 'complement system'.{European Medicines Agency (EMA), 2021 #1898;Dixon, 2023 #1862;de Castro, 2020 #1922;Xu, 2023 #1921;electronic Medicines Compendium (eMC), 2022 #1860} In an in-vitro study, pegcetacoplan prevented the formation of AP C3 and C5 convertases and inhibited the activity of both pre-formed convertases.[7,8] It also decreased the prolonged convertase activity mediated by C3NeF and C5NeF.[7,8] The activation of these convertases leads to C3b production and the formation of the membrane attack complex that is associated with renal function impairment.[8] Pegcetacoplan may mitigate complement-mediated kidney damage in C3G and other glomerular diseases in which complement may have a pathogenic role (such as IC-MPGN) by preventing excessive glomerular deposition of C3 and C5 breakdown products and the ensuing glomerular inflammation and renal damage observed in this disease.[4,9]

Pegcetacoplan is in clinical development for the treatment of C3G or primary IC-MPGN. It is intended to be administered as a subcutaneous infusion of 20ml (1080 mg), twice weekly for adults and adolescents weighing greater than 50 kg, and three other weight-based doses of either 10 ml (540 mg), 12 ml (648 mg), or 15 ml (810 mg).[1]

Key Innovation

With current treatment, about 50% of C3G and IC-MPGN patients progress to end-stage renal disease within 5 - 10 years of the diagnosis.[10] The treatment of IC-MPGN or C3G is centred on ameliorating the underlying immune dysregulation as well as minimizing the complications of hypertension and proteinuria.[11] There is to date no specific treatment of C3G and primary IC-MPGN, which directly targets the initial driver of the disease, C3, and possibly immunoglobulins deposition.[12] Complement inhibition such as C3 inhibition are promising strategies currently being explored in these populations.[10,13] However, no complement inhibitor has been approved to treat either disease to date.[13,14] There is a high need for targeted therapies such as complement inhibition to improve the prognosis of both conditions.[10]

Pegcetacoplan is one of only two low-molecular-weight C3 inhibitors that have advanced through clinical development.[7] The results of a phase II study (NOBLE study) studying the safety and security of pegcetacoplan in C3G, showed some efficacy in reducing proteinuria and a favorable safety profile.[4,7] If licensed, pegcetacoplan will offer an additional treatment option for patients with C3G and primary IC-MPGN who currently have few effective therapies available.

Regulatory & Development Status

Pegcetacoplan currently has marketing authorisation in the UK for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) in patients who are anaemic after treatment with a C5 inhibitor for at least 3 months.[2]

Pegcetacoplan has the following regulatory designations:

- Orphan drug designation in the EU for the treatment of C3 glomerulopathy with or without immune complexes in November 2022.[15]
- Orphan drug designation in the EU for the treatment of C3 glomerulopathy in 2019.[16]

Pegcetacoplan is currently in phase II/III clinical development for the treatment of:[17]

- Transplant-associated thrombotic microangiopathy
- Geographic atrophy secondary to age-related macular degeneration
- Paroxysmal (nocturnal) haemoglobinuria

Patient Group

Disease Area and Clinical Need

Membranoproliferative glomerulonephritis (MPGN) is an immune system disorder that causes damage to the tiny filters in the kidney (glomeruli) that help filter out waste and extra water in the body to form urine and retain blood and protein in the body.[18,19] It occurs due to a fault in the body's immune system that causes antibodies and a substance called complement (C3) to be deposited in the kidneys.[19] This affects the kidneys' ability to filter blood and can eventually lead to a reduction of kidney function.[19] C3 glomerulopathy (C3G) and primary IC-MPGN are both subtypes of MPGN.[11] Dysregulation of the complement alternative pathway, driven by acquired and/or genetic defects, plays a pathogenetic role in C3G and primary IC-MPGN and is likely the primary driver of disease.{Dixon, 2023 #1862;Donadelli, 2018 #1897;Donadelli, 2018 #1897}[22] The deposition of immune complexes, which results from paraproteinemias, autoimmune diseases, or chronic infections is the norm for primary IC-MPGN.[22] The common drivers of primary IC-MPGN and C3G are the C3 nephritic factors that bind to C3 convertase complex C3bBb, the key amplifying enzyme of the complement alternative pathway that cleaves C3 to C3a and C3b.[9] C3G and primary IC-MPGN symptoms are blood in the urine (haematuria), protein in the urine (proteinuria), swelling of different body parts (oedema), high blood pressure, etc.[19] In C3G and primary IC-MPGN, men and women are affected equally.[19,23]

MPGN affects around 1 in 100,000 people in the UK, while C3G, a subtype of MPGN, affects around 1 in 500,000 people in the UK.{Kidney care UK, 2023 #1880;Kidney Care UK, 2023 #1881;} No UK-specific stats for IC-MPGN were found. No UK-specific stats for IC-MPGN were found. In England 2022 – 23, there were 370 Finished Consultant Episodes (FCE) and 343 admissions for chronic nephritic syndrome (ICD-10 code N03 - includes glomerular disease, glomerulonephritis, and nephritis[25]) which resulted in 615 FCE bed days and 234 day cases.[26]

Recommended Treatment Options

There are no National Institute for health and Care Excellence (NICE) recommended treatment options for C3G and IC-MPGN.

Clinical Trial Information

Trial	NCT04572854, EudraCT 2020-002637-15; An Open-Label, Randomized, Controlled, Phase 2 Study to Evaluate the Safety and Efficacy of Pegcetacoplan in the Treatment of Post-Transplant Recurrence of C3G or IC-MPGN. **Phase II** – Ongoing **Location(s):** Five EU countries, UK, USA, and other countries **Primary completion date:** February 2023
Trial Design	Randomised, parallel assignment, open label.
Population	N = 13; subjects with clinical and pathologic evidence of recurrent C3G or IC-MPGN; aged at least 18 years.
Intervention(s)	Pegcetacoplan treatment of 1080 mg (under the skin) twice weekly will be given throughout the entire study.
Comparator(s)	No intervention given during the randomized controlled portion of the study (through week 12). After week 12, subjects will receive pegcetacoplan treatment.
Outcome(s)	Primary outcome: • The primary efficacy endpoint is the proportion of subjects with reduction in C3c staining on renal biopsy after 12 weeks of treatment with pegcetacoplan [time frame: 12 weeks after randomization] See trial record for full list of other outcomes
Results (efficacy)	At Week 12, of the 10 patients (IC-MPGN: n=2; C3G: n=8) treated with pegcetacoplan:[28] • Eight (80%) patients showed a reduction in C3c staining (reflective of damage-causing deposits) by one or more orders of magnitude of intensity from baseline. • Five (50%) patients showed a reduction in C3c staining by two or more orders of magnitude of intensity from baseline. • Four (40%) patients showed zero staining intensity, indicating that C3c deposits were cleared.
Results (safety)	There were no discontinuations/deaths due to treatment-emergent adverse events.[28]

Clinical Trial Information	
Trial	NCT05067127, EudraCT 2020-003767-25; A Phase 3, Randomized, Placebo-Controlled, Double-Blinded, Multicenter Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients With C3 Glomerulopathy or Immune-Complex Membranoproliferative Glomerulonephritis. **Phase III** – Ongoing **Location(s):** Nine EU countries, UK, USA, Canada and other countries

	Primary completion date: June 2024
Trial Design	Randomised, parallel assignment, triple masking
Population	N = 124 subjects with a diagnosis of primary C3G or IC-MPGN (with or without previous renal transplant); aged at least 18 years, where approved, adolescents (aged 12 to 17 years) weighing at least 30kg
Intervention(s)	Pegcetacoplan administered under the skin twice weekly
Comparator(s)	Placebo administered under the skin twice weekly
Outcome(s)	Primary outcome: • The log-transformed ratio of uPCR at week 26 compared to baseline. [Time frame: baseline to week 26] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information

Trial	NCT05809531, EudraCT2022-002833-33; An Open-Label, Nonrandomized, Multicenter Extension Study to Evaluate the Long-term Safety and Efficacy of Pegcetacoplan in Patients With C3 Glomerulopathy or Immune-Complex Membranoproliferative Glomerulonephritis. **Phase III** – ongoing **Location (s):** Five (5) EU countries, UK, USA and others **Primary completion date:** July 2027
Trial Design	Non-randomised, single group assignment, open-label
Population	N = 100 (planned); subjects who completed participation in study APL2-C3G-310 (NCT05067127 above) through the week 52 visit requirement; aged 12 years and older
Intervention(s)	Pegcetacoplan administered under the skin twice weekly according to protocol defined dosing regimen
Comparator(s)	None
Outcome(s)	Primary outcome The log-transformed ratio of urine protein-to-creatinine ratio (uPCR) over time compared to pretreatment baseline See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Pegcetacoplan is already marketed in the UK for the treatment of PNH; 1 vial of pegcetacoplan 54mg per ml costs £3,100.[29]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Iptacopan for treating complement 3 glomerulopathy (GID-TA11331). Expected publication date: TBC

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Eculizumab in the treatment of recurrence of C3 glomerulopathy post kidney transplant (all ages). 16054/P. February 2017.
- NHS England. Clinical Commissioning Policy Statement: Eculizumab in the prevention of recurrence of C3 glomerulopathy post kidney transplant. A06/PS/a. July 2015.

Other Guidance

- Rovin B., Adler S., Barratt J., Bridoux F., Burdge K., Chan T., et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. September 2021.[27]
- NICE Evidence Summary. C3 glomerulopathy in the native kidney: eculizumab (ESUOM49). 2015.
- NICE Evidence Summary. Prevention of recurrence of C3 glomerulopathy post-transplant: eculizumab (ESUOM44). 2015.

Additional Information

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