1. NAME OF THE MEDICINAL PRODUCT

ASPAVELI 1080 mg solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 mL vial contains 1080 mg of pegcetacoplan.
Each mL contains 54 mg of pegcetacoplan.

Excipients with known effect

Each mL contains 41 mg of sorbitol.
Each vial contains 820 mg of sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion

Clear, colourless to slightly yellowish aqueous solution with pH 5.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ASPAVELI is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia.

ASPAVELI is indicated for the treatment of adult and adolescent patients aged 12 to 17 years with C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN) in combination with a renin-angiotensin system (RAS) inhibitor, unless RAS inhibitor treatment is not tolerated or contraindicated.

4.2 Posology and method of administration

Therapy should be initiated under the supervision of a healthcare professional experienced in the management of patients with haematological or renal disorders.

Posology

PNH

Adult patients with PNH
Pegcetacoplan is administered twice weekly as a 1080 mg subcutaneous infusion with a commercially available syringe system infusion pump or on-body delivery system, that can deliver doses up to 20 mL. The twice weekly dose should be administered on Day 1 and Day 4 of each treatment week.

Treatment with pegcetacoplan is recommended to continue for the patient's lifetime, unless the discontinuation of this medicinal product is clinically indicated (see section 4.4).

Patients with PNH switching to pegcetacoplan from a C5 inhibitor
For the first 4 weeks, pegcetacoplan is administered as twice weekly subcutaneous doses of 1080 mg in addition to the patient's current dose of C5 inhibitor treatment to minimise the risk of haemolysis with abrupt treatment discontinuation. After 4 weeks, the patient should discontinue C5 inhibitor before continuing on monotherapy with this medicinal product.

Switches from complement inhibitors other than eculizumab have not been studied. Discontinuing other complement inhibitors before reaching steady-state of pegcetacoplan should be done with caution (see section 5.2).

Dose adjustment in PNH
The dosing regimen may be changed to 1080 mg every third day (e.g., Day 1, Day 4, Day 7, Day 10, Day 13, and so forth) if a patient has a lactate dehydrogenase (LDH) level greater than 2 x upper limit of normal (ULN). In the event of a dose increase, LDH should be monitored twice weekly for at least 4 weeks (see section 4.4).

C3G and primary IC-MPGN
Pegcetacoplan is administered twice weekly as a subcutaneous infusion with a commercially available syringe system infusion pump or on-body delivery system, that can deliver doses up to 20 mL. The twice weekly dose should be administered on Day 1 and Day 4 of each treatment week.

C3G and primary IC-MPGN are chronic diseases. Discontinuation of this medicinal product is not recommended unless clinically indicated.

Adult patients with C3G or primary IC-MPGN
Pegcetacoplan is administered twice weekly as a 1080 mg subcutaneous infusion.

Adolescent patients with C3G or primary IC-MPGN
For adolescent patients, the dosing regimen is based on the patient´s body weight and consists of the following:

Body weight	**First dose (infusion volume)**	**Second dose (infusion volume)**	**Maintenance dose (infusion volume)**
≥ 50 kg	1080 mg twice weekly (20 mL)		
35 to < 50 kg	648 mg (12 mL)	810 mg (15 mL)	810 mg twice weekly (15 mL)
30 to < 35 kg	540 mg (10 mL)	540 mg (10 mL)	648 mg twice weekly (12 mL)

Missed dose
If a dose of pegcetacoplan for treatment of PNH, C3G or primary IC-MPGN is missed, it should be administered as soon as possible, then the regular schedule should be resumed even if this results in an interval of less than 3 days between the replacement dose and the subsequent dose.

Patients with post-transplant recurrent C3G or primary IC-MPGN
Diagnosis of post-transplant recurrent C3G or primary IC-MPGN should be made based on a renal allograft biopsy. C3G or primary IC-MPGN recurrence may be detected in a routine post-transplant biopsy; otherwise, a biopsy should be performed when clinical signs indicate recurrent disease. As done in study APL2-C3G-204 (see section 5.1), treatment with pegcetacoplan can be started before the onset of clinical signs such as estimated glomerular filtration rate (eGFR) decrease or urine to protein-to-creatinine ratio (uPCR) increase. There is limited experience with the use of pegcetacoplan in patients with recurrent C3G or primary IC-MPGN after transplantation in clinical studies (see section 5.1).

Special populations

Elderly
Although there were no apparent age-related differences observed in clinical studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients. There is no evidence indicating any special precautions are required for treating an elderly population.

Renal impairment
Dose adjustment in patients with severe renal impairment (creatinine clearance <30 mL/min) is not necessary. There are no data available for the use of pegcetacoplan in patients with end-stage renal disease (ESRD) requiring dialysis (see section 5.2).

Hepatic impairment
The safety and efficacy of pegcetacoplan have not been studied in patients with hepatic impairment; however, no dose adjustment is recommended, as hepatic impairment is not expected to impact clearance of pegcetacoplan.

Paediatric population
The safety and efficacy of ASPAVELI in children with PNH aged 0 to <18 years have not yet been established. No data are available.

The safety and efficacy of ASPAVELI in children with C3G or primary IC-MPGN aged below 12 years have not been established. No data are available.

Method of administration

Pegcetacoplan should only be administered via subcutaneous administration using a commercially available syringe system infusion pump or on-body delivery system.

Pegcetacoplan can be given by a healthcare professional or administered by the patient or caregiver following proper instruction.

Self-administration and home infusion should be considered for patients who have tolerated treatment well in experienced treatment centres. The decision of a possibility of self-administration and home infusions should be made after evaluation and recommendation from the treating physician.
When self-administration is initiated, the patient will be instructed by a qualified healthcare professional in infusion techniques, the use of a syringe system infusion pump or an on-body delivery system, the keeping of a treatment record, the recognition of possible adverse reactions, and measures to be taken in case these occur.

When using a syringe system infusion pump, it should be infused in the abdomen, thighs, hips, or upper arms. Infusion sites should be at least 7.5 cm apart from each other. The infusion sites should be rotated between administrations. The infusion time is approximately 30 minutes (if using two sites) or approximately 60 minutes (if using one site).

When using an on-body delivery system, this medicinal product should be infused at a site on the abdomen. The infusion site should be rotated between administrations following the device manufacturer´s instructions. The infusion time varies by patient and typically ranges from 30 to 60 minutes.

Infusion into areas where the skin is tender, bruised, red, or hard should be avoided. Infusion into tattoos, scars, or stretch marks should be avoided. The infusion should be started promptly after drawing this medicinal product into the syringe. Administration should be completed within 2 hours

after preparing the syringe. For instructions on the preparation and infusion of the medicinal product, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pegcetacoplan therapy must not be initiated in patients:

- with unresolved infection caused by encapsulated bacteria including *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* (see section 4.4).
- who are not currently vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination (see section 4.4).

4.4 Special warnings and precautions for use

Serious infections caused by encapsulated bacteria

The use of pegcetacoplan may predispose individuals to serious infections caused by encapsulated bacteria including *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. To reduce the risk of infection, all patients must be vaccinated against these bacteria according to applicable local guidelines at least 2 weeks prior to receiving pegcetacoplan, unless the risk of delaying therapy outweighs the risk of developing an infection.

Patients with known history of vaccination
Before receiving treatment with pegcetacoplan, in patients with a known history of vaccination, it should be ensured that patients have received vaccines against encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* Type B within 2 years prior to starting pegcetacoplan.

Patients without known history of vaccination
For patients without known history of vaccination, the required vaccines should be administered at least 2 weeks prior to receiving the first dose of pegcetacoplan. If immediate therapy is indicated, the required vaccines should be administered as soon as possible and the patient treated with appropriate antibiotics until 2 weeks after vaccination.

Monitoring patients for serious infections
Vaccination may not be sufficient to prevent serious infection. Consideration should be given to official guidance on the appropriate use of antibacterial agents. All patients should be monitored for early signs of infections caused by encapsulated bacteria including *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, evaluated immediately if infection is suspected, and treated with appropriate antibiotics if necessary. Patients should be informed of these signs and symptoms, and steps taken to seek medical care immediately. Physicians must discuss the benefits and risks of pegcetacoplan therapy with patients.

Hypersensitivity

Hypersensitivity reactions have been reported (see section 4.8). If a severe hypersensitivity reaction (including anaphylaxis) occurs, infusion with pegcetacoplan must be discontinued immediately, and appropriate treatment instituted.

Injection site reactions

Injection site reactions have been reported with the use of subcutaneous pegcetacoplan (see section 4.8). Patients should be trained appropriately in proper injection technique.

PNH laboratory monitoring

Patients with PNH receiving pegcetacoplan should be monitored regularly for signs and symptoms of haemolysis, including measuring LDH levels, and may require dose adjustment within the recommended dosing schedule (see section 4.2).

Effects on laboratory tests

There may be interference between silica reagents in coagulation panels and pegcetacoplan that results in artificially prolonged activated partial thromboplastin time (aPTT); therefore, the use of silica reagents in coagulation panels should be avoided.

Treatment discontinuation for PNH

If patients with PNH discontinue treatment with pegcetacoplan, they should be closely monitored for signs and symptoms of serious intravascular haemolysis. Serious intravascular haemolysis is identified by elevated LDH levels along with sudden decrease in PNH clone size or haemoglobin (Hb), or reappearance of symptoms such as fatigue, haemoglobinuria, abdominal pain, dyspnoea, major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. If discontinuation of this medicinal product is necessary, alternate therapy should be considered. If serious haemolysis occurs after discontinuation, consider the following procedures/treatments: blood transfusion (packed RBCs), exchange transfusion, anticoagulation, and corticosteroids. Patients should be closely monitored for at least 8 weeks from the last dose, representing more than 5 half-lives of this medicinal product, to allow for medicinal product washout (see section 5.2) to detect serious haemolysis and other reactions. In addition, slow weaning should be considered.

Contraception in women of childbearing potential

It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with pegcetacoplan and for at least 8 weeks after the last dose of pegcetacoplan (see section 4.6).

Polyethylene glycol (PEG) accumulation

ASPAVELI is a PEGylated medicinal product. The potential long-term effects of PEG accumulation in the kidneys, the choroid plexus of the brain, and other organs are unknown (see section 5.3). Regular laboratory testing of renal function is recommended.

Educational materials

All physicians who intend to prescribe pegcetacoplan must ensure they have received and are familiar with the physician educational material. Physicians must explain and discuss the benefits and risks of pegcetacoplan therapy with the patient and provide them with the patient information pack and the patient card. The patient should be instructed to seek prompt medical care if they experience any sign or symptom of serious infection or hypersensitivity during therapy with pegcetacoplan, especially if indicative of infection with encapsulated bacteria.

Excipients with known effect

Sorbitol
This medicinal product contains 820 mg sorbitol in each vial. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Based on *in vitro* data, pegcetacoplan has low potential for clinical drug-drug interactions.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with pegcetacoplan and for at least 8 weeks after the last dose of pegcetacoplan. For women planning to become pregnant, the use of pegcetacoplan may be considered following an assessment of the risks and benefits (see Pregnancy).

Pregnancy

There is a limited amount of data from the use of pegcetacoplan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Pegcetacoplan is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether pegcetacoplan is excreted in human milk. The potential for absorption and harm to the breastfed infant is unknown. Animal data suggest a low excretion (less than 1%, not pharmacologically significant) of pegcetacoplan in monkey milk (see section 5.3). It is unlikely that a breastfed infant would have clinically relevant exposure.

It is recommended to discontinue breast-feeding during pegcetacoplan treatment.

Fertility

No animal or human data on the effect of pegcetacoplan on fertility are available. In toxicity studies, there were no microscopic abnormalities in male or female reproductive organs in monkeys (see section 5.3).

4.7 Effects on ability to drive and use machines

ASPAVELI has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

PNH
The most commonly reported adverse reactions in patients with PNH treated with pegcetacoplan are injection site reactions: injection site erythema (29%), injection site pruritus (13%), injection site swelling (12%), injection site pain (8%), injection site bruising (10%), upper respiratory tract infection (26%), diarrhoea (18%), haemolysis (19%), abdominal pain (19%), headache (18%), fatigue (15%), pyrexia (14%), cough (11%), urinary tract infection (9%), vaccination complication (11%),

pain in extremity (12%), dizziness (10%), arthralgia (10%) and back pain (8%). The most serious adverse reactions are haemolysis and sepsis.

C3G and primary IC-MPGN
The most commonly reported adverse reactions in patients with C3G or primary IC-MPGN treated with pegcetacoplan are infusion site reactions (33%) and upper respiratory tract infections (33%). The most serious adverse reactions are acute kidney injury (13%) and pneumonia (9%).

Tabulated list of adverse reactions

Table 1 gives the adverse reactions observed from the clinical studies and postmarketing experience with pegcetacoplan in patients with PNH, C3G and primary IC-MPGN. Adverse reactions are listed by MedDRA system organ class (SOC) and frequency, using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100) or rare (≥1/10 000 to <1/1 000), very rare (<1/10 000), and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions

MedDRA System Organ Class **Adverse reaction**	**Frequency in PNH**	**Frequency in C3G or primary IC-MPGN**
Infections and infestations		
Influenza		Very common
Upper respiratory tract infections[1]	Very common	Very common
Urinary tract infection	Very common	Common
Sepsis	Common[2]	
Opportunistic infections		Common[3]
COVID-19	Common	
Gastrointestinal infection	Common	
Fungal infection	Common	
Skin infection	Common	
Oral infection	Common	
Ear infection	Common	Common
Infection	Common	
Respiratory tract infection[4]	Common	
Viral infection	Common	
Bacterial infection	Common	
Vaginal infection	Common	
Eye infection	Common	
Cervicitis	Uncommon	
Groin infection	Uncommon	
Pneumonia	Uncommon	Common
Nasal abscess	Uncommon	
Tuberculosis	Uncommon	
Oesophageal candidiasis	Uncommon	
COVID-19 pneumonia	Uncommon	
Anal abscess	Uncommon	
Blood and lymphatic system disorders		
Haemolysis	Very common	
Thrombocytopenia	Common	Common[5]
Neutropenia	Common	Common
Immune system disorders		
Hypersensitivity reaction		Very common[6]
Metabolism and nutrition disorders		

MedDRA System Organ Class Adverse reaction	Frequency in PNH	Frequency in C3G or primary IC-MPGN
Hypokalaemia	Common	Common
Nervous system disorders		
Headache	Very common	Very common
Dizziness	Very common	
Vascular disorders		
Hypertension	Common	
Respiratory, thoracic and mediastinal disorders		
Cough	Very common	Common
Dyspnoea	Common	
Oropharyngeal pain	Common	
Nasal congestion	Common	
Epistaxis	Common	Common
Gastrointestinal disorders		
Abdominal pain	Very common	
Diarrhoea	Very common	Very common
Nausea	Common	Very common
Skin and subcutaneous tissue disorders		
Erythema	Common	
Rash	Common	
Urticaria	Common	
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	
Back pain	Very common	
Pain in extremity	Very common	Common
Myalgia	Common	Common
Muscle spasms	Common	
Renal and urinary disorders		
Acute kidney injury	Common	Very common
Chromaturia	Common	
General disorders and administration site conditions		
Pyrexia	Very common	Very common
Fatigue	Very common	Common
Infusion site reactions[7]	Very common	Very common
Investigations		
Alanine aminotransferase increased	Common	
Bilirubin increased	Common	
Injury, poisoning and procedural complications		
Vaccination complication	Very common	

[1]Include nasopharyngitis, upper respiratory tract infection, pharyngitis, rhinitis and sinusitis.
[2]Sepsis includes one case of septic shock and one case with non-encapsulated *Neisseria meningitidis*.
[3]*Herpes zoster* (including *Herpes zoster meningoencephalitis*), and *Pneumocystis jirovecii* infection.
[4]Include respiratory tract infection and respiratory tract infection viral.
[5]Includes decreased platelet count.
[6]Include rash and eczema.
[7]PTs included in Infusion site reactions: infusion site erythema, infusion site pruritus, infusion site swelling, infusion site bruising, infusion site pain, infusion site induration.

Description of selected adverse reactions

Infections
Forty-eight patients experienced an infection during Study APL2-302 in PNH patients. The most frequent infections in patients treated with pegcetacoplan during Study APL2-302 were upper

respiratory tract infection (28 cases, 35%). Most infections reported in patients treated with pegcetacoplan during Study APL2-302 were nonserious, and predominantly mild in intensity. Ten patients developed infections reported as serious including one patient who died due to COVID-19. The most frequent serious infections were sepsis (3 cases) (leading to discontinuation of pegcetacoplan in one patient) and gastroenteritis (3 cases); all of which resolved.

In C3G and primary IC-MPGN clinical studies, four serious respiratory tract infections caused by encapsulated bacteria were reported in patients treated with pegcetacoplan: an epiglottitis, a pneumococcal pneumonia and an atypical pneumonia that led to interruption, and a pneumonia *Haemophilus* with no dose adjustment. Events recovered and resolved except for the events of pneumonia *Haemophilus* and the atypical pneumonia that resolved with sequelae. In addition, one serious *Escherichia* urinary tract infection was reported, the event recovered and resolved with no dose adjustment.

Haemolysis
Nineteen patients reported haemolysis during Study APL2-302 in PNH patients treated with pegcetacoplan. Seven cases were reported as serious, and 5 cases led to discontinuation of pegcetacoplan and the dose of pegcetacoplan was increased in 10 patients. There were 3 non-serious cases of haemolysis during Study APL2-308 in PNH patients treated with pegcetacoplan, none of which led to discontinuation of pegcetacoplan The dose of pegcetacoplan was increased in all 3 patients.

Acute kidney injury
In C3G and primary IC-MPGN clinical studies, 10 serious events of acute kidney injury were reported in 8 patients (5.7%) treated with pegcetacoplan, of which 5 events were observed in 4 post-transplant patients. Of these serious events, only 1 led to drug withdrawal and 1 to dose interruption. All events recovered and resolved, except the single event that led to drug withdrawal.

Patients with post-transplant recurrent C3G or primary IC-MPGN
In the patients with post-transplant recurrent C3G or primary IC-MPGN (N=22), included in Studies APL2-C3G-310 and APL2-C3G-204, the safety profile appeared consistent with that of the overall population.

Paediatric population

In adolescent patients with C3G or primary IC-MPGN (N=28, aged 12 years to 17 years) included in Study APL2-C3G-310, the safety profile appeared consistent with the overall results. The most common adverse reactions reported in this patient population were infusion site reactions.
The safety of pegcetacoplan has not been studied in paediatric patients less than 12 years of age.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

In the postmarketing setting, cases of overdose have been reported, with no new safety events observed. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Complement inhibitors, ATC code: L04AJ03

Mechanism of action

Pegcetacoplan is a symmetrical molecule comprised of two identical pentadecapeptides covalently bound to the ends of a linear 40-kDa PEG molecule. The peptide moieties bind to complement C3 and C3b and exert a broad inhibition of the complement cascade. The 40-kDa PEG moiety imparts improved solubility and longer residence time in the body after administration of the medicinal product.

Pegcetacoplan binds to complement protein C3 and its activation fragment C3b, thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation. In PNH, extravascular haemolysis (EVH) is facilitated by C3b opsonisation while intravascular haemolysis (IVH) is mediated by the downstream membrane attack complex (MAC). Pegcetacoplan exerts broad regulation of the complement cascade by acting proximal to both C3b and MAC formation, thereby controlling the mechanisms that lead to EVH and IVH.

In C3G and primary IC-MPGN, there is excessive deposition of C3 breakdown products in the glomeruli of the kidney leading to renal parenchymal damage and impairment of kidney function. Pegcetacoplan targets upstream effectors of complement activation (C3 and C3b), thereby inhibiting activation initiated by all (alternative, classical and lectin) complement pathways. By inhibiting C3, pegcetacoplan directly addresses the inappropriate C3 activation and modifies the underlying disease by reducing the excessive deposition of C3 breakdown products in the glomeruli of the kidney. By targeting C3b, pegcetacoplan also inhibits the activity of the alternative pathway (AP) C3 convertase through an additional mechanism of action in the complement cascade. This further prevents deposition of C3 breakdown products in the glomeruli.

Pharmacodynamic effects

PNH
In Study APL2-302, the mean serum C3 concentration increased from 0.94 g/L at baseline to 3.83 g/L at Week 16 in the pegcetacoplan group and sustained through Week 48. In Study APL2-308, the mean serum C3 concentration increased from 0.95 g/L at baseline to 3.56 g/L at Week 26.

In Study APL2-302, the mean percentage of PNH Type II + III RBCs increased from 66.80% at baseline, to 93.85% at Week 16 and sustained through Week 48. In Study APL2-308, the mean percentage of PNH Type II + III RBCs increased from 42.4% at baseline to 90.0% at Week 26.

In Study APL2-302, the mean percentage of PNH Type II + III RBCs with C3 deposition was decreased from 17.73% at baseline to 0.20% at Week 16 and sustained through Week 48. In Study APL2-308, the mean percentage of PNH Type II + III RBCs with C3 deposition decreased from 2.85% at baseline to 0.09% at Week 26.

C3G and primary IC-MPGN
In Study APL2-C3G-310, the mean serum C3 concentration increased from 0.62 g/L at baseline to 3.71 g/L at Week 26 in the pegcetacoplan group and the effect was sustained up to Week 52. In the placebo group, C3 concentrations remained stable up to Week 26 (0.57 g/L at baseline; 0.58 g/L at Week 26) and increased upon switch to pegcetacoplan to 3.59 g/L at Week 52.

Mean serum sC5b-9 concentration decreased from 902.5 ng/mL at baseline to 290.2 ng/mL at Week 26 in the pegcetacoplan group and the effect was sustained up to Week 52. In the placebo group, sC5b-9 concentrations remained stable (768.3 ng/mL at baseline; 759.9 ng/mL at Week 26) and decreased upon switch to pegcetacoplan to 272.9 ng/mL at Week 52.

Clearance of glomerular C3 deposits at 6 months was observed based on a greater proportion of patients achieving a staining score of zero in the pegcetacoplan (71.4%) as compared to the placebo (8.8%) group.

Clinical efficacy and safety

PNH
The efficacy and safety of pegcetacoplan in patients with PNH was assessed in two open-label, randomised-controlled phase 3 studies: in complement inhibitor-experienced patients in Study APL2-302 and in complement inhibitor-naïve patients in Study APL2-308. In both studies the dose of pegcetacoplan was 1080 mg twice weekly. If required, the dose could be adjusted to 1080 mg every 3 days.

Study in complement inhibitor-experienced adult patients (APL2-302)
Study APL2-302 was an open-label, randomised study with an active comparator-controlled period of 16 weeks followed by a 32-week open label period (OLP). This study enrolled patients with PNH who had been treated with a stable dose of eculizumab for at least the previous 3 months and with Hb levels <10.5 g/dL. Eligible patients entered a 4-week run-in period during which they received pegcetacoplan 1080 mg subcutaneously twice weekly in addition to their current dose of eculizumab. Patients were then randomised in a 1:1 ratio to receive either 1080 mg of pegcetacoplan twice weekly or their current dose of eculizumab through the duration of the 16-week randomised controlled period (RCP). Randomisation was stratified based on the number of packed red blood cell (PRBC) transfusions within the 12 months prior to Day -28 (<4; ≥4) and platelet count at screening (<100 000/mm^3; ≥100 000/mm^3). Patients who completed the RCP entered the OLP during which all patients received pegcetacoplan for up to 32 weeks (patients who received eculizumab during the RCP entered a 4-week run-in period before switching to pegcetacoplan monotherapy).

The primary and secondary efficacy endpoints were assessed at Week 16. The primary efficacy endpoint was change from baseline to Week 16 (during RCP) in Hb level. Baseline was defined as the average of measurements prior to the first dose of pegcetacoplan (at the beginning of the run-in period). Key secondary efficacy endpoints were transfusion avoidance, defined as the proportion of patients who did not require a transfusion during the RCP, and change from baseline to Week 16 in absolute reticulocyte count (ARC), LDH level, and functional assessment of chronic illness therapy (FACIT)-Fatigue scale score.

A total of 80 patients entered the run-in period. At the end of the run-in period, all 80 were randomised, 41 to pegcetacoplan and 39 to eculizumab. Demographics and baseline disease characteristics were generally well balanced between treatment groups (see Table 2). A total of 38 patients in the group treated with pegcetacoplan and 39 patients in the eculizumab group completed the 16-week RCP and continued into the 32-week open-label period. In total, 12 of 80 (15%) patients receiving pegcetacoplan discontinued due to adverse events. Per protocol 15 patients had their dose adjusted to 1080 mg every 3 days. Twelve patients were evaluated for benefit and 8 of the 12 patients demonstrated benefit from the dose adjustment.

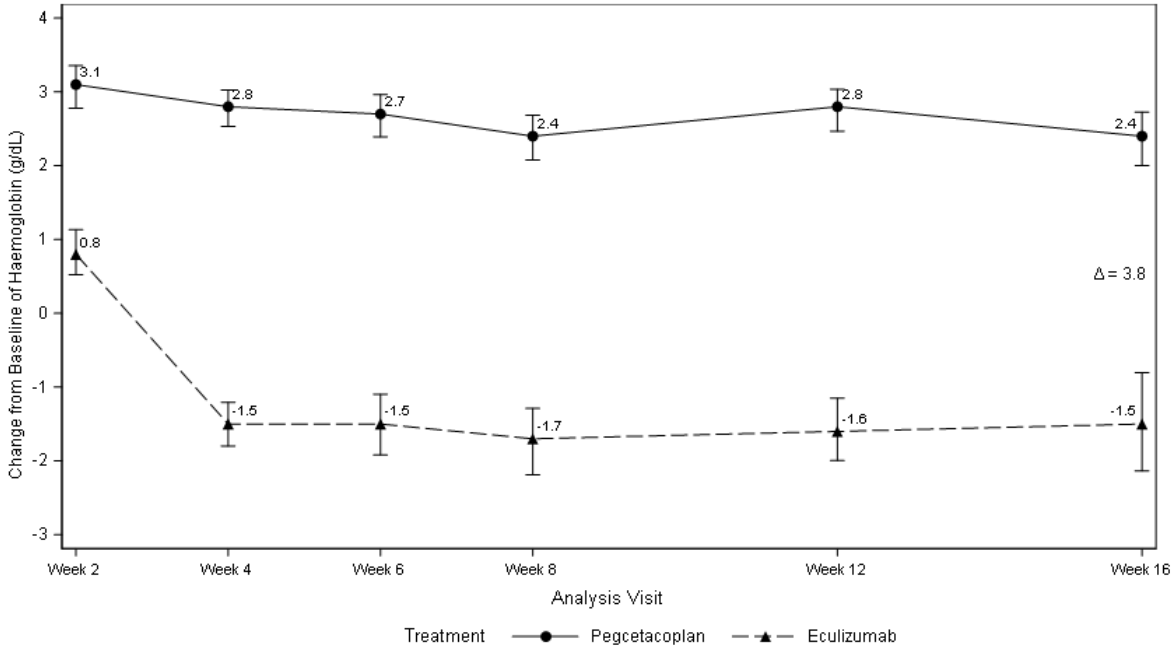
Table 2: Patient baseline demographics and characteristics in Study APL2-302

Parameter	Statistics	Pegcetacoplan (N=41)	Eculizumab (N=39)
Age (years)	Mean (SD)	50.2 (16.3)	47.3 (15.8)
18-64 years	n (%)	31 (75.6)	32 (82.1)
≥65 years	n (%)	10 (24.4)	7 (17.9)
Dose level of eculizumab at baseline			
Every 2 weeks IV 900 mg	n (%)	26 (63.4)	29 (74.4)
Every 11 days IV 900 mg	n (%)	1 (2.4)	1 (2.6)
Every 2 weeks IV 1 200 mg	n (%)	12 (29.3)	9 (23.1)
Every 2 weeks IV 1 500 mg	n (%)	2 (4.9)	0
Female	n (%)	27 (65.9)	22 (56.4)
Time since diagnosis of PNH (years) to Day -28	Mean (SD)	8.7 (7.4)	11.4 (9.7)
Haemoglobin level (g/dL)	Mean (SD)	8.7 (1.1)	8.7 (0.9)
Reticulocyte count (10^9/L)	Mean (SD)	218 (75.0)	216 (69.1)
LDH level (U/L)	Mean (SD)	257.5 (97.6)	308.6 (284.8)
Total FACIT-Fatigue*	Mean (SD)	32.2 (11.4)	31.6 (12.5)
Number of transfusions in last 12 months prior to Day -28	Mean (SD)	6.1 (7.3)	6.9 (7.7)
<4	n (%)	20 (48.8)	16 (41.0)
≥4	n (%)	21 (51.2)	23 (59.0)
Platelet count at screening (10^9/L)	Mean (SD)	167 (98.3)	147 (68.8)
Platelet count at screening <100 000/mm^3	n (%)	12 (29.3)	9 (23.1)
Platelet count at screening ≥100 000/mm^3	n (%)	29 (70.7)	30 (76.9)
History of aplastic anaemia	n (%)	11 (26.8)	9 (23.1)
History of myelodysplastic syndrome	n (%)	1 (2.4)	2 (5.1)

*FACIT-Fatigue is measured on a scale of 0-52, with higher values indicating less fatigue.

Pegcetacoplan was superior to eculizumab for the primary endpoint of the haemoglobin change from baseline (P<0.0001).

Figure 1. Adjusted mean change in haemoglobin (g/dL) from baseline to Week 16 in APL2-302



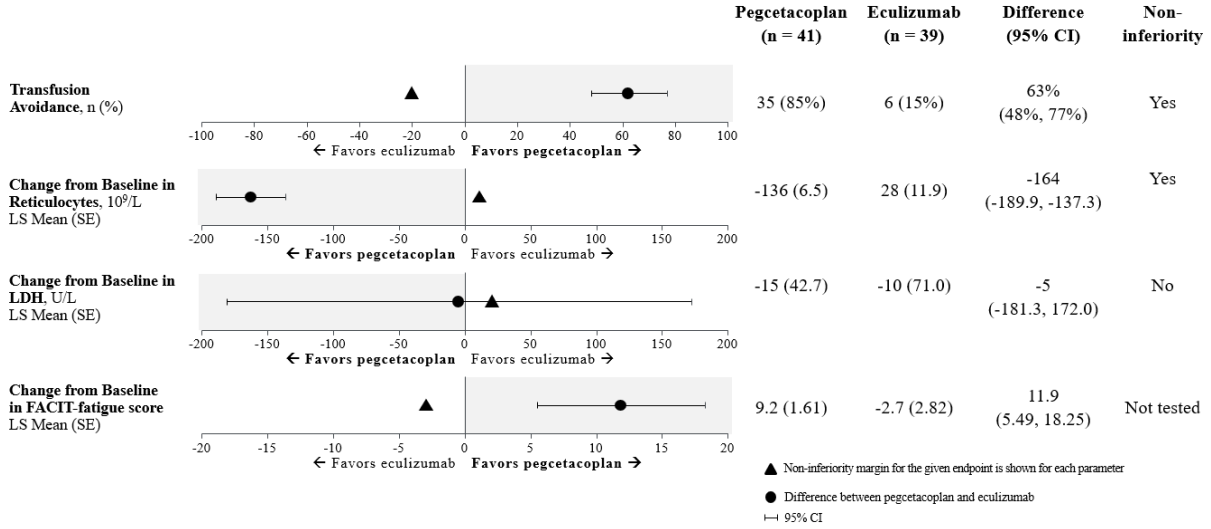
Non-inferiority was demonstrated in key secondary endpoints of transfusion avoidance and change from baseline in ARC.

Non-inferiority was not met in change from baseline in LDH.

Due to hierarchical testing, statistical testing for change from baseline for FACIT-Fatigue score was not formally tested.

The adjusted means, treatment difference, confidence intervals, and statistical analyses performed for the key secondary endpoints are shown in Figure 2.

Figure 2. Key secondary endpoints analysis in APL2-302



Results were consistent across all supportive analyses of the primary and key secondary endpoints, including all observed data with post transfusion data included.

Hb normalisation was achieved in 34% of patients in the pegcetacoplan group versus 0% in the eculizumab group at Week 16. LDH normalisation was achieved in 71% of patients in the group treated with pegcetacoplan versus 15% in the eculizumab group.

A total of 77 patients entered the 32-week OLP, during which all patients received pegcetacoplan, resulting in a total exposure of up to 48 weeks. The results at Week 48 were generally consistent with those at Week 16 and support sustained efficacy.

Study in complement inhibitor-naïve adult patients (APL2-308)
Study APL2-308 was an open-label, randomised, controlled study that enrolled patients with PNH who had not been treated with any complement inhibitor within 3 months prior to enrolment and with Hb levels less than the lower limit of normal (LLN). Eligible patients were randomised in a 2:1 ratio to receive pegcetacoplan or supportive care (e.g., transfusions, corticosteroids, supplements such as iron, folate, and vitamin B12), hereafter referred to as the control arm through the duration of the 26-week treatment period.

Randomisation was stratified based on the number of PRBC transfusions within the 12 months prior to Day -28 (<4; ≥4). At any point during the study, a patient assigned to the control arm who had Hb levels ≥2 g/dL below baseline or presented with a PNH associated thromboembolic event was per protocol able to transition to pegcetacoplan for the remainder of the study.

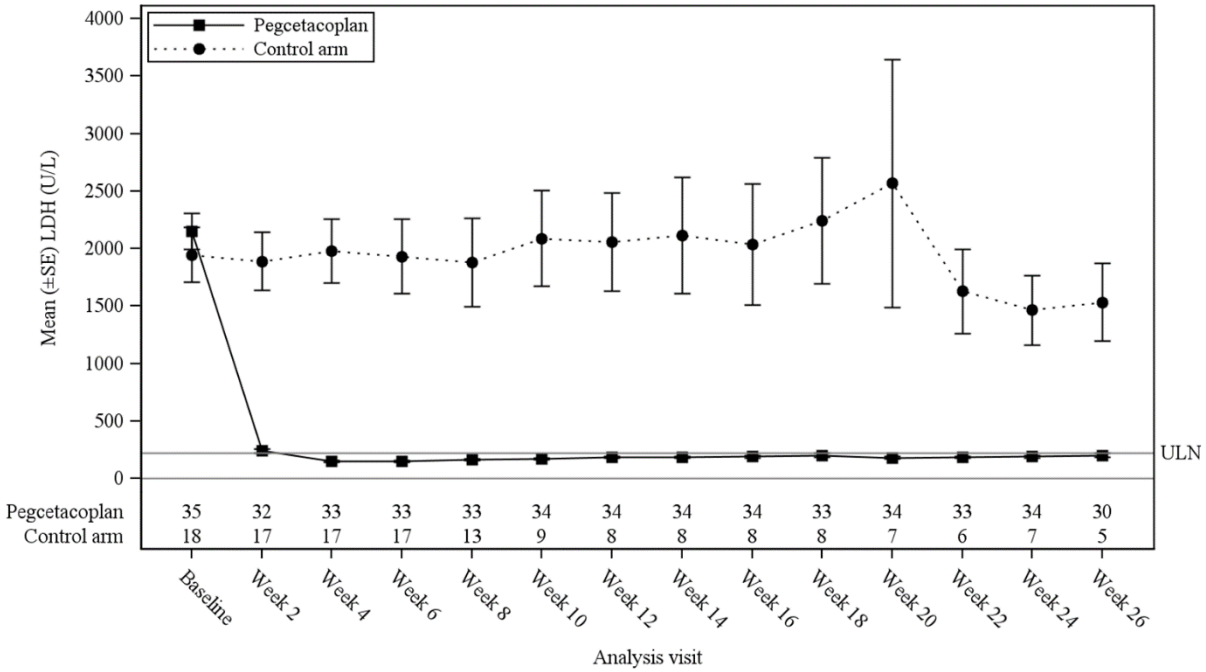
A total of 53 patients were randomised, 35 to pegcetacoplan and 18 patients to the control arm. Demographics and baseline disease characteristics were generally well balanced between treatment arms. The mean age was 42.2 years in the pegcetacoplan arm and 49.1 years in the control arm. The mean number of PRBC transfusions in the 12 months prior to screening was 3.9 in the pegcetacoplan arm and 5.1 in the control arm. Five patients in each arm (14.3% in the pegcetacoplan arm and 27.8% in the control arm) had a history of aplastic anaemia. Further baseline values were as follows: mean baseline Hb levels (pegcetacoplan arm: 9.4 g/dL vs. control arm; 8.7 g/dL), ARC (pegcetacoplan arm: 230.2×10^9/L vs. control arm: 180.3×10^9/L), LDH (pegcetacoplan arm: 2 151.0 U/L vs. control arm: 1 945.9 U/L) and platelet count (pegcetacoplan arm: 191.4×10^9/L vs. control arm: 125.5×10^9/L). Eleven of 18 patients randomised to the control arm transitioned to pegcetacoplan because their Hb levels decreased by ≥2 g/dL below baseline. Of the 53 randomised patients, 52 (97.8%) received prophylactic antibiotic therapy according to local prescribing guidelines.

The primary and secondary efficacy endpoints were assessed at Week 26. The two co-primary efficacy endpoints were Hb stabilisation, defined as avoidance of a >1 g/dL decrease in Hb concentration from baseline in the absence of transfusion, and change in LDH concentration from baseline.

In the group treated with pegcetacoplan, 30 out of 35 patients (85.7%) achieved Hb stabilisation versus 0 patients in the control arm. The adjusted difference between pegcetacoplan and the control arm was 73.1% (95% CI, 57.2% to 89.0%; p<0.0001).

The least-square (LS) mean (SE) changes from baseline in LDH concentration at Week 26 were -1 870 U/L in the group treated with pegcetacoplan versus -400 U/L in the control arm (p<0.0001). The difference between pegcetacoplan and the control arm was -1 470 (95% CI, -2 113 to -827). Treatment differences between the pegcetacoplan and the control arm were evident at Week 2 and were maintained through Week 26 (Figure 3). LDH concentrations in the control arm remained elevated.

Figure 3. Mean (±SE) LDH concentration (U/L) over time by treatment group in study APL2-308



For the selected key secondary efficacy endpoints of haemoglobin response in the absence of transfusions, change in haemoglobin level, and change in ARC, the group treated with pegcetacoplan demonstrated a significant treatment difference versus the control arm (Table 3).

Table 3: Key secondary endpoints analysis in study APL2-308

Parameter	Pegcetacoplan (N=35)	Control arm (N=18)	Difference (95% CI) p-value
Haemoglobin response in the absence of transfusions[a] n (%)	25 (71%)	1 (6%)	54% (34%, 74%) $p < 0.0001$
Change from baseline to Week 26 in haemoglobin level (g/dL) LS Mean (SE)	2.9 (0.38)	0.3 (0.76)	2.7 (1.0, 4.4)
Change from baseline to Week 26 in ARC (10^9/L) LS Mean (SE)	-123 (9.2)	-19 (25.2)	-104 (-159, -49)

[a] Haemoglobin response was defined as a ≥1 g/dL increase in haemoglobin from baseline at Week 26.
ARC = Absolute reticulocyte count, CI = Confidence interval, LS = Least square, SE = Standard error

C3G and primary IC-MPGN
The efficacy and safety of pegcetacoplan in patients with C3G or primary IC-MPGN was assessed in the randomised, placebo-controlled, double- blinded phase 3 Study APL2-C3G-310, including adults and adolescents with native kidney or post-transplant recurrent C3G or primary IC-MPGN.

The dose of pegcetacoplan was 1080 mg twice weekly for adults or adolescents with body weights ≥50 kg, or weight-based for adolescents with body weights <50 kg.

Study in adult and adolescent patients with C3G or primary IC-MPGN (APL2-C3G-310)
Study APL2-C3G-310 was a randomised, double-blinded study with a placebo-controlled period of 26-weeks, followed by a 26-week OLP. This study enrolled adolescents from 12 years to 17 years of age, and adults with C3G or primary IC-MPGN. This study enrolled patients with native kidney or post-transplant recurrent disease who presented with proteinuria ≥1 g/day and eGFR ≥30 mL/min/1.73 m^2. Patients were on a stable and optimised dose regimen for C3G/primary IC-MPGN treatment (e.g., RAS inhibitors, sodium-glucose cotransporter-2 [SGLT-2] inhibitors, immunosuppressants, systemic corticosteroids no higher than 20 mg/day of prednisone equivalent) for at least 12 weeks prior to randomisation.

Eligible patients were randomised in a 1:1 ratio to receive pegcetacoplan or placebo subcutaneously twice weekly during the 26-week RCP. Two stratification factors were applied to the randomisation; patients with post-transplant recurrence versus native kidney disease patients, and patients with baseline renal biopsies (either collected during screening or within 28 weeks prior to randomisation) versus patients without baseline renal biopsies. During the RCP, changes to the baseline treatment regimens for C3G/primary IC-MPGN were minimised and only made when required for the well-being of the patient. Patients who completed the RCP, entered the 26-week OLP, in which all participants were treated with pegcetacoplan twice weekly.

A total of 124 patients were randomised, 63 to pegcetacoplan and 61 to placebo. Demographics and baseline disease characteristics were generally balanced between the two groups (see Table 4). A total of 118 patients completed the 26-week RCP, of which 114 patients completed the OLP treatment period with pegcetacoplan (N=59 pegcetacoplan-to-pegcetacoplan; N=55 placebo-to-pegcetacoplan).

Table 4: Patient baseline demographics and disease characteristics in study APL2-C3G-310

Parameter	Statistics	Pegcetacoplan (N=63)	Placebo (N=61)
Age (years)	Mean (SD)	28.2 (17.1)	23.6 (14.3)
Adolescents (12 – 17 years)	n (%)	28 (44.4)	27 (44.3)
Adults ≥18 years	n (%)	35 (55.6)	34 (55.7)
Sex			
Male	n (%)	26 (41.3)	28 (45.9)
Female	n (%)	37 (58.7)	33 (54.1)
Type of disease at Screening			
C3G	n (%)	51 (81.0)	45 (73.8)
C3GN	n (%)	45 (71.4)	41 (67.2)
DDD	n (%)	4 (6.3)	4 (6.6)
Undetermined	n (%)	2 (3.2)	0
IC-MPGN	n (%)	12 (19.0)	16 (26.2)
Time since diagnosis of C3G/IC-MPGN (years)	Mean (SD)	3.64 (3.47)	3.76 (3.62)
Prior kidney transplant	n (%)	5 (7.9)	4 (6.6)
Time since last kidney transplant (years)	Mean (SD)	11.4 (6.7)	5.8 (6.4)
Time since most recent post-transplant recurrence (years)	Mean (SD)	1.47 (1.49)	1.38 (1.64)
Baseline triplicate FMU uPCR (mg/g)	Mean (SD)	3124 (2408)	2541 (2015)
Baseline eGFR (mL/min/1.73 m^2)	Mean (SD)	78.5 (34.1)	87.2 (37.2)
C3c staining in baseline biopsy			
3+	n (%)	51 (81.0)	51 (83.6)
2+	n (%)	12 (19.0)	10 (16.4)
Baseline serum albumin (g/dL)	Mean (SD)	3.31 (0.61)	3.39 (0.70)
Baseline serum C3 (mg/dL)	Mean (SD)	60.6 (45.7)	56.3 (35.6)
Disease manifestations			
Oedema	n (%)	45 (71.4)	32 (52.5)
Fatigue	n (%)	16 (25.4)	8 (13.1)
Haematuria	n (%)	37 (58.7)	39 (63.9)
High Blood Pressure	n (%)	35 (55.6)	29 (47.5)
Nephrotic Syndrome	n (%)	32 (50.8)	27 (44.3)
Use of other treatments at baseline*			
Agents acting on the renin-angiotensin system	n (%)	59 (93.7)	54 (88.5)
Immunosuppressants	n (%)	49 (77.8)	45 (73.8)
Glucocorticoids	n (%)	29 (46.0)	27 (44.3)

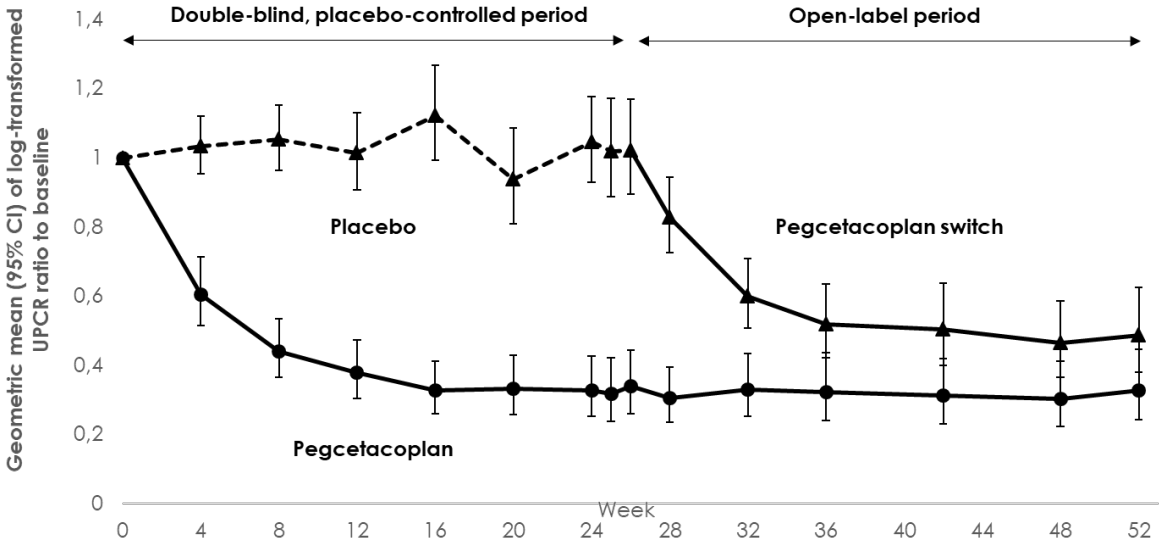
*Within 12 weeks prior to study entry.
C3G = C3 glomerulopathy, C3GN = C3 glomerulonephritis, DDD = Dense-deposit disease, IC MPGN = Immune-complex membranoproliferative glomerulonephritis, FMU = First-morning urine, uPCR = Urine protein-to-creatinine ratio, eGFR = Estimated glomerular filtration rate, SD = Standard deviation

The primary and key secondary efficacy endpoints were assessed at Week 26. The primary efficacy endpoint was the log-transformed ratio of first-morning urine (FMU) uPCR at Week 26 compared with baseline.

Pegcetacoplan was superior to placebo, with a statistically significant 68.1% reduction (95% CI: 57.3% to 76.2%, p<0.0001) in uPCR from baseline compared to placebo after 26 weeks of treatment (-67.2% [95% CI: -74.9% to -57.2%] and + 2.9% [95% CI: -8.6% to 15.9%] for pegcetacoplan and placebo respectively. Efficacy of similar magnitude was observed in subgroups irrespective of age (adolescents vs. adults), disease type (C3G vs. primary IC-MPGN), disease status (native vs. post-transplant recurrent disease), and concomitant use of immunosuppressants/glucocorticoids (yes vs. no). The effect of pegcetacoplan on uPCR was sustained through Week 52 (-67.2 % from

baseline). Patients who switched from placebo to pegcetacoplan at Week 26 (Figure 4) experienced a similar reduction (-51.3%) at Week 52.

Figure 4. Geometric mean ratio (95% CI) of FMU uPCR compared to baseline over time by treatment group from MMRM model in Study APL2-C3G-310



Note: Geometric mean ratio calculated from re-exponentiated LS Means.
CI = Confidence interval, LS = Least square, FMU = First-morning urine, uPCR = Urine protein-to-creatinine ratio, MMRM = Mixed model of repeated measure

Pegcetacoplan treatment for 26 weeks demonstrated statistically significant improvement in the key secondary endpoint related to proteinuria reduction, with 60.3% of patients treated with pegcetacoplan achieving a ≥50% reduction in uPCR compared to 4.9% in the placebo group, a difference of 52.7% (95% CI: 29.2%–76.2%; p<0.0001).

Pegcetacoplan treatment for 26 weeks resulted in a higher proportion of patients achieving a reduction of two orders of magnitude or greater, on a scale of 0-3, in renal C3 staining intensity with 26 (74.3%) patients on pegcetacoplan vs. 4 (11.8%) on placebo and a difference of 64.3% (95% CI: 41.4% - 87.2%, nominal p<0.0001).

Pegcetacoplan treatment for 26 weeks showed stabilisation in eGFR with a change from baseline of -1.497 (2.242) on pegcetacoplan vs. -7.808 (1.919) on placebo, and a treatment difference of 6.312 mL/min/1.73m^2 (95% CI: 0.501, 12.122, nominal p=0.0333). The effect of pegcetacoplan on eGFR was sustained through Week 52. Patients who switched from placebo to pegcetacoplan at Week 26 experienced a similar stabilisation at Week 52.

Efficacy of similar magnitude was broadly observed for proteinuria reduction ≥50%, C3 staining clearance and eGFR stabilisation in subgroups irrespective of age (adolescents vs. adults), disease type (C3G vs. primary IC-MPGN), disease status (native vs. post-transplant recurrent disease) and concomitant use of immunosuppressants/glucocorticoids (yes vs. no) at Week 26.

Study in adult post-transplant recurrent C3G or primary IC-MPGN (APL2-C3G-204)
Study APL2-C3G-204 was a phase 2 open-label, randomised study in 13 adult patients with post-transplant recurrent C3G (N=10) or primary IC-MPGN (N=3) for 52 weeks.

During the first 12 weeks of the study, 10 patients received pegcetacoplan, in addition to standard of care (SOC), and 3 only SOC. All patients received pegcetacoplan from Week 13 to Week 52.

The primary endpoint of reduction in C3 staining intensity on renal biopsy at Week 12 was observed in 50% of the patients treated with pegcetacoplan (5 of 10 patients; 4 of which, achieved a staining score of zero), and 33.3% of the patients in the control group (1 of 3 patients; with this patient achieving a staining score of 1).

In general, changes and percentage changes from baseline in eGFR (secondary endpoint) were small. Mean (SD) eGFR changed from 52.3 (12.11) mL/min/1.73 m^2 at baseline to 57.3 (25.12) mL/min/1.73 m^2 at Week 52, and median eGFR changed from 50.5 mL/min/1.73 m^2 at baseline to 58.5 mL/min/1.73 m^2 at Week 52. Most patients (9 of 13 patients [69.2%]) across groups achieved stabilisation or improvement in eGFR by Week 52.

Immunogenicity

Two different assays for the detection of anti-pegcetacoplan peptide anti-drug antibody (ADA) were used in PNH and C3G or primary IC-MPGN clinical studies, respectively. The assay used for C3G or primary IC-MPGN was more sensitive. Differences in assays preclude meaningful comparisons of the incidence of ADAs in the studies described below.

In PNH clinical studies, ADA incidence (treatment-emergent ADA or boosted ADA from pre-existing level) was low, and when present, had no noticeable impact on the PK/PD, efficacy, or safety profile of pegcetacoplan. Throughout studies APL2-302 and APL2-308, 3 out of 126 patients who were exposed to pegcetacoplan had confirmed positive anti-pegcetacoplan peptide antibodies. All 3 patients also tested positive for neutralising antibody (NAb). NAb response had no apparent impact on PK or clinical efficacy. Eighteen out of 126 patients developed anti-PEG antibodies; 9 were treatment-emergent and 9 were treatment-boosted.

In C3G and primary IC-MPGN clinical studies, ADA incidence (treatment-emergent ADA or boosted ADA from pre-existing level) in study APL2-C3G-310 was 23.6% for anti-PEG and 16.3% for anti-pegcetacoplan peptide. Based on population PK and PD analysis, ADAs had no clinically meaningful impact on efficacy or PK/PD in a pooled analysis population. Five patients also tested positive for NAb. NAb response had no apparent impact on PK or clinical efficacy. Twenty-nine out of 123 patients developed anti-PEG antibodies;14 were treatment-emergent and 15 were treatment-boosted. In patients with post-transplant recurrent disease in study APL2-C3G-204, no patient developed a positive ADA response (treatment-emergent ADA or boosted ADA from pre-existing level) to pegcetacoplan peptide or PEG. During the 26-week placebo-controlled period in study APL2-C3G-310, there was no detectable impact of ADAs on the safety of pegcetacoplan treatment.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with this medicinal product in one or more subsets of the paediatric population in PNH and C3G or primary IC-MPGN, respectively (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Pegcetacoplan is administered by subcutaneous infusion and gradually absorbed into the systemic circulation with a median T_{max} between 108 and 144 hours (4.5 to 6.0 days) following a single subcutaneous dose to healthy volunteers.

Steady-state serum concentrations following twice weekly dosing at 1080 mg in patients with PNH were achieved approximately 4 to 6 weeks following the first dose. In complement inhibitor-experienced patients (Study APL2-302) the geometric mean (%CV) steady-state serum concentrations ranged between 655 (18.6%) and 706 (15.1%) µg/mL in patients treated for 16 weeks. Steady-state

concentrations in the patients (n=22) that continued to receive pegcetacoplan up to Week 48 were 623 µg/mL (39.7%), indicating sustainable therapeutic concentrations of pegcetacoplan through Week 48. In complement inhibitor-naïve patients (Study APL2-308) the geometric mean (%CV) steady-state serum concentration at Week 26 was 744 µg/mL (25.5%) with twice weekly dosing. The bioavailability of a subcutaneous dose of pegcetacoplan is estimated to be 76% based on population PK analysis.

Steady-state serum concentrations following twice weekly dosing at 1080 mg in C3G or primary IC-MPGN patients were achieved approximately 4 to 8 weeks following the first dose and therapeutic concentrations of pegcetacoplan were maintained through Week 52. In patients of study APL2-C3G-310, the steady-state mean (%CV) serum concentrations ranged between 715.8 (31.2%) and 765.7 (23.2%) µg/mL up to Week 26 and remained between 670.1 (30.1%) and 726.6 (30.5%) µg/mL up to Week 52.

Distribution

The mean (%CV) volume of distribution of pegcetacoplan is approximately 3.98 L (32%) in patients with PNH based on population PK analysis.

The mean (%CV) of central volume of distribution of pegcetacoplan is approximately 4.31 L (32.1%) in adult patients with C3G or primary IC-MPGN.

Biotransformation/

Based on its PEGylated peptide structure, the metabolism of pegcetacoplan is expected to occur via catabolic pathways and be degraded into small peptides, amino acids, and PEG. Results of a radiolabelled study in cynomolgus monkeys suggest the primary route of elimination of the labelled peptide moiety is via urinary excretion. Although the elimination of PEG was not studied, it is known to undergo renal excretion.

Pegcetacoplan showed no inhibition or induction of the CYP enzyme isoforms tested as demonstrated from the results of *in vitro* studies. Pegcetacoplan was neither a substrate nor an inhibitor of the human uptake or efflux transporters.

Elimination

Following multiple subcutaneous dosing of pegcetacoplan in patients with PNH, the mean (%CV) clearance is 0.015 L/h (30%) and median effective half-life of elimination ($t_{1/2}$) is 8.6 days as estimated by the population PK analysis.

The estimated mean (CV%) of clearance is 0.012 L/hour (43%) in adult patients with C3G or primary IC-MPGN. The median terminal $t_{1/2}$ is 10.1 days in adult patients with C3G or primary IC-MPGN.

Linearity/non-linearity

Exposure of pegcetacoplan increases in a dose proportional manner from 45 to 1440 mg.

Special populations

Effects of age, weight, gender or race
No impact on the pharmacokinetics of pegcetacoplan was identified with age (12-81 years), race or sex based on the results of population PK analysis in patients with PNH, C3G or primary IC-MPGN.

Compared with a reference 70 kg patient, the steady-state average concentration is predicted to be approximately 20% higher in patients with a body weight of 50 kg. PNH patients weighing 40 kg are

predicted to have a 45% higher average concentration. Minimal data are available on the safety profile of pegcetacoplan for PNH patients with a body weight below 50 kg.

Elderly
Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 years and over is not sufficient to determine whether they respond differently from younger patients. See section 4.2.

Paediatric population
Based on population PK analysis, body weight in adolescent patients (12-17 years) has an impact on clearance and volume of distribution. The dosing regimen for adolescents with C3G or primary IC-MPGN is based on the patient´s body weight. See section 4.2. The model-predicted exposure for adolescents with C3G or primary IC-MPGN is adequately matched to the adult reference exposure.

Renal impairment
In a study of 8 patients with severe renal impairment, defined as creatinine clearance (CrCl) less than 30 mL/min using the Cockcroft-Gault formula (with 4 patients with values less than 20 mL/min), renal impairment had no effect on the pharmacokinetics of a single 270-mg dose of pegcetacoplan. There are minimal data on patients with PNH with renal impairment who have been administered the clinical dose of 1080 mg twice weekly. Based on population PK analysis, eGFR had no clinically meaningful impact on pegcetacoplan exposure in a pooled analysis population. There are no available clinical data for the use of pegcetacoplan in patients with ESRD requiring dialysis. See section 4.2.

5.3 Preclinical safety data

In vitro and *in vivo* toxicology data reveal no toxicity of special concern for humans. Effects observed in animals at exposure levels similar to clinical exposure levels are described below. These effects were not observed in clinical studies.

Reproductive and developmental toxicity

Pegcetacoplan treatment of pregnant cynomolgus monkeys at a subcutaneous dose of 28 mg/kg/day (2.9 times the human steady-state C_{max}) from the gestation period through parturition resulted in a statistically significant increase in abortions or stillbirths. No maternal toxicity or teratogenic effects were observed in offspring delivered at term. Additionally, no developmental effects were observed in infants up to 6 months postpartum. Systemic exposure to pegcetacoplan was detected in foetuses from monkeys treated with 28 mg/kg/day from the period of organogenesis through the second trimester, but the exposure was minimal (less than 1%, not pharmacologically significant).

Carcinogenesis

Long term animal carcinogenicity studies of pegcetacoplan have not been conducted.

Genotoxicity

Pegcetacoplan was not mutagenic when tested in *in vitro* bacterial reverse mutation (Ames) assays and was not genotoxic in an *in vitro* assay in human TK6 cells or in an *in vivo* micronucleus assay in mice.

Animal toxicology

Repeat-dose studies were conducted in rabbits and cynomolgus monkeys with daily subcutaneous doses of pegcetacoplan up to 7 times the human dose (1080 mg twice weekly). Histologic findings in both species included dose-dependent epithelial vacuolation and infiltrates of vacuolated macrophages in multiple tissues. These findings have been associated with large cumulative doses of long-chain

PEG in other marketed PEGylated drugs, were without clinical consequence, and were not considered adverse. Reversibility was not demonstrated in the pegcetacoplan animal studies after one month and was not evaluated for a longer duration. Data from literature suggest reversibility of PEG vacuoles.

Renal tubular degeneration was observed microscopically in both species at exposures (C_{max} and AUC) less than or comparable to those for the human dose and was minimal and nonprogressive between 4 weeks and 9 months of daily administration of pegcetacoplan. Although no overt signs of renal dysfunction were observed in animals, the clinical significance and functional consequence of these findings are unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E 420)
Glacial acetic acid
Sodium acetate trihydrate
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Store in the original carton in order to protect from light.

6.5 Nature and contents of container

A Type I glass vial with a stopper (chlorobutyl or bromobutyl), and a seal (aluminium) with a flip-off cap (polypropylene) containing 54 mg/mL of sterile solution.

Each single pack contains 1 vial.

Multipack containing 8 (8 packs of 1) vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product comes as a ready-to-use solution in single-use vials. Because the solution contains no preservative, this medicinal product should be infused immediately after preparing the syringe.

This medicinal product is a clear, colourless to slightly yellowish aqueous solution. Do not use if the liquid looks cloudy, contains particles, or is dark yellow.

Always bring the vial to the room temperature for approximately 30 minutes before use.

Remove the protective flip cap from the vial to expose the central portion of the gray rubber stopper of the vial. Clean the stopper with a new alcohol wipe and allow the stopper to dry. Do not use if the protective flip cap is missing or damaged.

Preparing the syringe

Option 1: If using a needleless transfer device (such as a vial adapter), follow the instructions provided by the device manufacturer.

Option 2: If transfer is done using a transfer needle and a syringe, follow the instructions below:

- Attach a sterile transfer needle to a sterile syringe.
- Pull back the plunger to fill the syringe with air, which should be about 20 mL.
- Make sure the vial is in upright position. Do not turn the vial upside down.
- Push the air-filled syringe with transfer needle attached through the centre of the vial stopper.
- The tip of the transfer needle should not be in the solution to avoid creating bubbles.
- Gently push the air from the syringe into the vial. This will inject the air from the syringe into the vial.
- Invert the vial.
- With the transfer needle tip in the solution, slowly pull the plunger to fill the syringe with the prescribed dose of ASPAVELI.
- Remove the filled syringe and the transfer needle from the vial.
- Do not recap the transfer needle. Unscrew the needle and throw it away in the sharps container.

Administration

This medicinal product should only be administered via subcutaneous administration using either a syringe system infusion pump or an on-body delivery system:

- Follow the device manufacturer's instructions to prepare the infusion pump and tubing. When using an infusion pump, areas for infusion include the abdomen, thighs, hips, or upper arms. Rotate infusion sites from one infusion to the next. If there are multiple infusion sites, they should be at least 7.5 cm apart. The infusion time is approximately 30 minutes (if using two sites) or approximately 60 minutes (if using one site).

- Follow the device manufacturer's instructions to prepare the on-body delivery system. When using the on-body delivery system, this medicinal product should be administered at a site on the abdomen. Rotate the infusion site from one infusion to the next. The infusion time varies by patient and typically ranges from 30 to 60 minutes.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1595/001
EU/1/21/1595/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 December 2021
Date of latest renewal: 20 July 2026

10. DATE OF REVISION OF THE TEXT

20/07/2026

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.