swissmedic

Date: 26 January 2026
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Aspaveli

International non-proprietary name:	pegcetacoplan
Pharmaceutical form:	solution for infusion
Dosage strength(s):	54 mg/mL
Route(s) of administration:	subcutaneous use
Marketing authorisation holder:	Swedish Orphan Biovitrum AG
Marketing authorisation no.:	68674
Decision and decision date:	extension of therapeutic indication approved on 4 December 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, definitions, abbreviations 3
2 Background information on the procedure 5
2.1 Applicant's request(s) and information regarding procedure 5
2.2 Indication and dosage 5
2.2.1 Requested indication 5
2.2.2 Approved indication 5
2.2.3 Requested dosage 5
2.2.4 Approved dosage 5
2.3 Regulatory history (milestones) 6
3 Medical context 7
4 Nonclinical aspects 7
5 Clinical aspects 8
5.1 Clinical pharmacology 8
5.2 Dose finding and dose recommendation 8
5.3 Efficacy 9
5.4 Safety 9
5.5 Final clinical benefit risk assessment 10
6 Risk management plan summary 11
7 Appendix 12

1 Terms, definitions, abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BW	Body weight
C3	Complement 3
C3G	Complement 3 glomerulopathy
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ERA	Environmental risk assessment
ESKD	End-stage kidney disease
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC-MPGN	Immune complex membranoproliferative glomerulonephritis
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MPGN	Membranoproliferative glomerulonephritis
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PEG	Polyethylene glycol
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PNH	Paroxysmal nocturnal haemoglobinuria
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RAAS	Renin-angiotensin-aldosterone system
RMP	Risk management plan
SAE	Serious adverse event
sC5b-9	soluble complement 5b-9
SwissPAR	Swiss Public Assessment Report

TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
uPCR	Urine protein-to-creatinine ratio

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved indication in accordance with Article 23 TPO.

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 15 May 2025.

2.2 Indication and dosage

2.2.1 Requested indication

Treatment of adults and adolescents aged 12 to 17 years with C3 glomerulopathy (C3G) or primary immune complex membranoproliferative glomerulonephritis (IC-MPGN).

2.2.2 Approved indication

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).

2.2.3 Requested dosage

Aspaveli is administered twice weekly as a subcutaneous infusion of 1080 mg in adult patients.

Adolescent patients with C3G or primary IC-MPGN
In adolescent patients, the dosage regimen is based on the patient's body weight and is as follows:

Body weight	First dose (Infusion volume)	Second dose (Infusion volume)	Maintenance dose (Infusion volume)
50 kg and above	1080 mg twice weekly (20 ml)		
35 to less than 50 kg	648 mg (12 ml)	810 mg (15 ml)	810 mg twice weekly (15 ml)
30 to less than 35 kg	540 mg (10 ml)	540 mg (10 ml)	648 mg twice weekly (12 ml)

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	13 May 2025
Formal control completed	19 May 2025
List of Questions (LoQ)	22 July 2025
Response to LoQ	3 September 2025
Preliminary decision	23 October 2025
Response to preliminary decision	25 November 2025
Final decision	4 December 2025
Decision	approval

3 Medical context

MPGN is a histologic pattern of immune-mediated glomerular injury rather than a single disease. IC-MPGN and C3G frequently progress to ESKD, especially with persistent proteinuria, low eGFR, or chronic damage, and often recur after transplantation. No approved therapies exist for C3G, making it a high-unmet-need condition and a key target for complement-directed treatments.

4 Nonclinical aspects

This is an authorisation application for the extension of the indication for Aspaveli with pegcetacoplan as the active ingredient. The company has not submitted any preclinical documentation except for an environmental risk assessment. This application for the extension of the indication is based on newly generated clinical data. As the maximum dose strength, route of administration, and dosing recommendation remain unchanged, the lack of additional preclinical documentation is acceptable. A definitive juvenile toxicity study in rats is still ongoing and is scheduled to be completed by April 2026. The updated environmental risk assessment can be accepted.
Efficacy for the proposed indication is to be clinically assessed.

From the Nonclinical Assessment perspective, there were no open questions based on the documentation submitted.

5 Clinical aspects

5.1 Clinical pharmacology

The new indication is for C3 glomerulopathy (C3G) in adults and adolescents aged 12 to 17 years.
The following posology is proposed:
Twice-weekly SC injection of 1080 mg (20 mL) using an injection pump.
In adolescents, BW band-based dosage is proposed, identical to what was studied in the pivotal study APL2-C3G-310:

- ≥50 kg 1080 mg twice a week
- 35 to < 50 kg: first dose 648 mg, second dose 810 mg, thereafter 810 mg twice a week
- 30 to <35 kg: first dose 540 mg, second dose 540 mg, thereafter 648 mg twice a week

Pharmacokinetics
Data from 3 clinical trials enrolling patients with C3G or primary IC-MPGN (APL2-201, APL2-C3G-204, APL2-C3G-310) were described in a pop PK analysis based on the reference model. The model described the data well.

Estimated pegcetacoplan exposure is lower for PNH patients compared to healthy subjects, C3G patients, and IC-MPGN. The median half-life of pegcetacoplan at a subcutaneous twice-weekly dose was estimated as 8.2 days for adult PNH patients, 9.9 days for healthy adults, 10.2 days for C3G patients, and 10.8 days for IC-MPGN patients. Exposure in patients with C3G or IC-MPGN was similar.

Observed serum pegcetacoplan concentrations were slightly lower for adolescents compared to adults; however, this did not correspond to a difference in uPCR response. While the 95th percentile and the median of the model predicted exposure for adolescents with C3G or IC-MPGN are within the adult exposure, the 5th percentile in adolescents seems lower. Thus, it has to be relied on efficacy data and not on a PK extrapolation.

Neither anti-PEG nor anti-peptide immunogenicity are expected to have a clinically meaningful impact on exposure to pegcetacoplan.

Pharmacodynamics
Treatment with pegcetacoplan resulted in a sustained increase in mean serum C3 concentrations and a decrease in mean plasma sC5b-9 concentrations. This is as expected for the mechanism of action of pegcetacoplan.

Based on the pegcetacoplan exposure / uPCR response model, the maximal achievable uPCR response for a C3G or IC-MPGN patient weighing 70 kg with baseline serum albumin of 3.5 g/dL was a 91% reduction from a population baseline uPCR of 1740 mg/g. The median pegcetacoplan serum $C_{avg,ss}$ of 840.5 µg/mL exceeds the IC_{50} for uPCR response (1.70-fold) and is predicted to achieve between 60% to 65% (−54.6% to −59.2% uPCR change from baseline) of the maximal achievable response. This supports the proposed posology.

Neither anti-PEG nor anti-peptide immunogenicity were predicted to have a clinically meaningful effect on uPCR response to pegcetacoplan treatment.

5.2 Dose finding and dose recommendation

The adult dosing regimen of pegcetacoplan 1080 mg SC twice weekly is based on prior clinical data in PNH (studies APL2-201, -302, -308) and aims to ensure effective systemic exposure with good

tolerability. In study APL2-201 (the first to include C3G patients), initial daily dosing (360 mg) was later transitioned to 1080 mg twice weekly. This dose selection was informed by nonclinical data, PK modelling, and the goal of reducing dosing burden.

5.3 Efficacy

Pegcetacoplan has been investigated across a structured phase 2–3 development programme in patients with C3 glomerulopathy (C3G) and primary immune-complex MPGN, including post-transplant recurrence, diseases with high unmet need and no approved therapies.

The pivotal phase 3 study APL2-C3G-310 (VALIANT) was a global, randomised, double-blind, placebo-controlled trial in adolescents and adults. Participants received pegcetacoplan 1080 mg subcutaneously twice weekly or placebo for 26 weeks, followed by open-label treatment. The study population was clinically relevant and heterogeneous, reflecting real-world disease, with balanced baseline characteristics and acceptable retention. The overall design is appropriate for a rare, progressive condition.

VALIANT met its primary endpoint, demonstrating a statistically significant and clinically meaningful 68% reduction in proteinuria at week 26 versus placebo, with effects observed early and consistently across subgroups. Key secondary endpoints supported efficacy, including a markedly higher composite renal response rate and clear stabilisation of eGFR compared with placebo. Histological findings were supportive: while changes in activity scores were modest, pegcetacoplan led to a pronounced reduction and frequent resolution of C3c staining, aligning with its mechanism of action. Benefits were maintained during the open-label phase, including in patients initially randomised to placebo.

Long-term data from the open-label extension study (APL2-C3G-314) indicate durable proteinuria reduction (~70%) and sustained renal function stability over more than one year, although the non-randomised design and selection based on “clinical benefit” may introduce potential bias. Earlier phase 2 studies in post-transplant disease (APL2-C3G-204) and exploratory cohorts (APL2-201) provide additional supportive evidence of biological and clinical activity, but are limited by small sample sizes and open-label designs.

Overall, the totality of evidence supports pegcetacoplan as a clinically effective and potentially disease-modifying therapy in C3G and primary IC-MPGN, with the strongest and most reliable data derived from the phase 3 VALIANT trial.

5.4 Safety

Across three studies (APL2-C3G-310, -204, and -201), the pegcetacoplan safety database included 168 patients with C3G or related conditions, ranging from adolescents to older adults and reflecting real-world background therapy, including frequent use of RAAS blockade and immunosuppression.
In the randomised phase 3 study APL2-C3G-310, adverse events were common, but occurred slightly less often with pegcetacoplan than with placebo (84.1% vs. 93.4%). Most events were mild to moderate. Rates of severe AEs, serious AEs, treatment-related AEs, and treatment discontinuations were comparable between groups, with no excess toxicity signal. No deaths occurred in the pegcetacoplan arm during the randomised phase.
Injection-site and infusion-related reactions were, as expected, more frequent with pegcetacoplan, but were generally mild and transient. Infections such as nasopharyngitis, influenza, and pyrexia were common, but mostly non-serious and balanced versus placebo. One isolated case of herpes zoster meningoencephalitis was reported as possibly related.

Exposure-adjusted analyses showed decreasing AE and infection rates over time, with no evidence of cumulative toxicity. Overall, the safety profile of pegcetacoplan appears acceptable and consistent with complement inhibition in a high-risk renal population.

5.5 Final clinical benefit risk assessment

Pegcetacoplan showed clinically meaningful efficacy in patients ≥12 years with C3G or primary IC-MPGN, with substantial proteinuria reduction, renal function stabilisation, and supportive histologic evidence of disease modification. Effects were sustained over time, supported by long-term but limited open-label data.
Safety was acceptable and comparable to placebo, with mostly mild to moderate adverse events and no cumulative toxicity. Overall, the benefit-risk balance is favourable in this high-unmet-need population.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Aspaveli was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

ASPAVELI

Composition

Active substances

Pegcetacoplan

Excipients

Sorbitol (E420), glacial acetic acid (E260), sodium acetate trihydrate (E262), sodium hydroxide (for pH adjustment) (E524), water for injection.

Contains sorbitol 41 mg/mL or 820 mg/vial respectively, and sodium max. 0.37 mg/mL or 7.4 mg/vial respectively.

Pharmaceutical form and active substance quantity per unit

Solution for infusion.

For subcutaneous administration.

One 20 mL vial contains 1080 mg of pegcetacoplan. 1 mL of solution for infusion contains 54 mg of pegcetacoplan.

Appearance

Clear, colourless to slightly yellowish aqueous solution with pH 5.0

Indications/Uses

Aspaveli is indicated:

- as monotherapy for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH), who have haemolytic anaemia (see *Dosage/Administration* and *Clinical efficacy*).
- 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).

Dosage/Administration

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

Aspaveli is intended for subcutaneous administration using a commercially available syringe system infusion pump and can be self-administered. Aspaveli should be infused in the abdomen, thigh, hips or upper arm region.

Self-administration and home infusion may 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.

PNH is a chronic disease and treatment with Aspaveli is recommended to continue for the patient's lifetime, unless the discontinuation of Aspaveli is clinically indicated (see *Warnings and precautions*).

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

Usual dosage

Aspaveli can be given by a healthcare professional or administered by the patient or caregiver following proper instructions.

Before receiving treatment with Aspaveli:

- 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 (Hib) within 2 years prior to starting Aspaveli (see *Warnings and precautions*).
- For patients without known history of vaccination: The required vaccines should be administered at least 2 weeks prior to receiving the first dose of Aspaveli (see *Warnings and precautions*).
    - If immediate therapy with Aspaveli is indicated, the required vaccines should be administered as soon as possible, and patients should be provided with 2 weeks of antibacterial drug prophylaxis (see *Warnings and precautions*).

PNH

Adult patients with PNH

Aspaveli is administered twice weekly as a 1080 mg subcutaneous infusion with a commercially available syringe system infusion pump 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 (see *Mode of administration*).

Patients with PNH switching to Aspaveli from C5 inhibitor

- For the first 4 weeks, Aspaveli is administered as twice weekly subcutaneous doses of 1080 mg in addition to the patient's current dose of C5 inhibitor treatment to minimize the risk of haemolysis with abrupt treatment discontinuation.

- After 4 weeks, the patient should discontinue C5 inhibitor and continue the treatment as monotherapy with Aspaveli.
- 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 *Pharmacokinetics*).

Dose adjustment in PNH

- The dosing regimen may be changed to 1080 mg every third day (i.e. 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 times upper limit of normal (ULN).
- In the event of a dose increase, monitor LDH twice weekly for at least 4 weeks.

C3G and primary IC-MPGN

Aspaveli is administered twice weekly as a subcutaneous infusion with a commercially available syringe system infusion pump 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.

Adult patients with C3G or primary IC-MPGN

Aspaveli 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:

Body weight	**First dose (infusion volume)**	**Second dose (infusion volume)**	**Maintenance dose (infusion volume)**
≥ 50 kg	1 080 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 Aspaveli for treatment of PNH, C3G or primary IC-MPGN is missed, it should be administered as soon as possible, and then treatment should be resumed with the regular schedule. Do not take more than one dose on the same day.

Patients with C3G or primary IC-MPGN after kidney transplantation (recurrent disease)

Diagnosis of 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 Clinical efficacy), 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-creatine ratio (uPCR) increase.

Special dosage instructions

Patients with hepatic disorders

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 (see *Pharmacokinetics*).

Patients with renal disorders

Severe renal impairment (creatinine clearance <30 mL/min) had no effect on the pharmacokinetics (PK) of pegcetacoplan; therefore, pegcetacoplan dose adjustment in patients with renal impairment is not necessary. There are no data available for the use of pegcetacoplan in patients with end stage renal disease (ESRD) requiring dialysis (see *Pharmacokinetics*).

Elderly patients

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

Children and adolescents

The safety and efficacy of pegcetacoplan in children with PNH from birth to under 18 years have not yet been established. No data are available.

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

Mode of administration

Aspaveli should only be administered via subcutaneous administration using a syringe system infusion pump able to achieve a nominal 20 mL delivered volume.

When Aspaveli treatment is initiated, the patient should be instructed by a qualified healthcare professional in infusion techniques, the use of a syringe system infusion pump, the keeping of a treatment record, the recognition of possible adverse reactions, and measures to be taken in case these occur.

Aspaveli should be administered via subcutaneous infusion 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 administration. Infusions into areas where the skin is tender, bruised, red, or hard and infusions into tattoos, scars, or stretch marks should be avoided.

The typical infusion time is approximately 30 minutes (if using two sites) or approximately 60 minutes (if using one site). The infusion should be started promptly after drawing Aspaveli into the syringe. Administration should be completed within 2 hours after preparing the syringe.

See *Instructions for handling* and *instruction for use* in the package leaflet for further instructions on the preparation and administration of the medicinal product.

Contraindications

Aspaveli is contra-indicated in patients with:

- hypersensitivity to pegcetacoplan or to any of the excipients.
- unresolved infection caused by encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*.
- 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 *Warnings and precautions*).

Warnings and precautions

Serious Infections Caused by Encapsulated Bacteria

The use of Pegcetacoplan may lead to serious infections caused by encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis*, 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 treatment, unless the risk of delaying therapy with pegcetacoplan 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.

Vaccination may not be sufficient to prevent serious infection. Consideration should be given to official guidance on the appropriate use of antibiotics. All patients should be monitored for early signs of infection 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.

Hypersensitivity

Hypersensitivity reactions have been reported. If a severe hypersensitivity reaction (including anaphylaxis) occurs, discontinue infusion with pegcetacoplan immediately and institute appropriate treatment.

Monitoring PNH Manifestations after Discontinuation of pegcetacoplan

If patients with PNH discontinue treatment with pegcetacoplan, they must 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, shortness of breath (dyspnoea), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. If discontinuation of pegcetacoplan is necessary, alternate therapy should be considered because PNH is life-threatening if untreated. 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, 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 *Pregnancy, lactation*).

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 *Preclinical data*). Regular laboratory testing of renal function is recommended.

Educational materials

All physicians who intend to prescribe ASPAVELI must ensure they have received and are familiar with the physician educational material. Physicians must explain and discuss the benefits and risks of ASPAVELI 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 ASPAVELI, especially if indicative of infection with encapsulated bacteria.

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.

Sorbitol

This medicinal product contains 820 mg sorbitol per 20 mL vial. Patients with hereditary fructose intolerance (HFI) must not receive this medicine.

Sodium

This medicine contains 7.4 mg sodium per 20 mL vial, that is to say, essentially 'sodium-free'.

Interactions

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

Pregnancy, 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 should only be considered following an assessment of the risks and benefits (see *Pregnancy*).

Pregnancy

There are no or limited data available on pegcetacoplan use in pregnant women. Studies in animals have shown reproductive toxicity (see *Preclinical data*).

Pegcetacoplan must not be used during pregnancy and in women of childbearing potential not using contraception, unless treatment with pegcetacoplan is required due to the clinical condition of the woman.

Lactation

It is not known whether pegcetacoplan is secreted in human milk. Minimal (less than 1%, not pharmacologically significant) pegcetacoplan excretion in milk has been demonstrated in monkeys. It is unlikely that a breastfed infant would have clinically relevant exposure (see *Preclinical data*).

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

Fertility

Effects of pegcetacoplan upon fertility have not been studied in animals. There were no microscopic abnormalities in male or female reproductive organs in toxicity studies in monkeys (see *Preclinical data*).

Effects on ability to drive and use machines

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

Undesirable effects

PNH

Summary of the safety profile

The most commonly reported adverse reactions in patients with PNH treated with pegcetacoplan were injection site reactions: injection site erythema, injection site pruritus, injection site swelling, injection site pain, injection site bruising. Other adverse reactions reported in more than 10% of patients during clinical studies were upper respiratory tract infection, diarrhoea, haemolysis, abdominal pain, headache, fatigue, pyrexia, cough, urinary tract infection, vaccination complication, pain in extremity, dizziness, arthralgia and back pain. The most commonly reported serious adverse reactions were haemolysis and sepsis.

Tabulated list of adverse reactions

Table 1 gives the adverse reactions observed from the clinical studies and from post-marketing experience with pegcetacoplan in patients with PNH. Adverse reactions are listed by MedDRA SOC and frequency categories are defined using the following convention: very common (≥ 1/10); common (≥1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (<1/10,000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions in patients with PNH from clinical trials[1] and postmarketing experience

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Very common	Upper respiratory tract infection Urinary tract infection
	Common	Sepsis[2] COVID-19 Gastrointestinal infection Fungal infection Skin infection Oral infection Ear infection Infection Respiratory tract infection Viral infection Bacterial infection Vaginal infection Eye infection
	Uncommon	Cervicitis Groin infection Pneumonia Nasal abscess Tuberculosis Oesophageal candidiasis COVID-19 pneumonia Anal abscess
Blood and lymphatic system disorders	Very common	Haemolysis
	Common	Thrombocytopenia Neutropenia
Immune system disorders	Uncommon	Anaphylactic reaction[3] Anaphylactic shock[3]
Metabolism and nutrition disorders	Common	Hypokalaemia
Nervous system disorders	Very common	Headache Dizziness
Vascular disorders	Common	Hypertension
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Dyspnoea Epistaxis Oropharyngeal pain Nasal congestion
Gastrointestinal disorders	Very common	Abdominal pain Diarrhoea
	Common	Nausea
Hepatobiliary disorders	Common	Alanine aminotransferase increased Bilirubin increased
Skin and subcutaneous tissue disorders	Common	Erythema Rash Urticaria
Musculoskeletal and connective tissue disorders	Very common	Arthralgia Back pain Pain in extremity
	Common	Myalgia Muscle spasms
Renal and urinary disorders	Common	Acute kidney injury Chromaturia

General disorders and administration site conditions	Very common	Injection site erythema Injection site pruritus Injection site swelling Injection site bruising Fatigue Pyrexia Injection site pain
	Common	Injection site reaction Injection site induration
Injury, poisoning and procedural complications	Very common	Vaccination complication[4]

[1] Studies APL2-302, APL2-308, APL2-202, APL2-204, and APL2-CP0514 in PNH patients. Medically similar terms are grouped, where appropriate, on the basis of similar medical concept.

[2] Sepsis includes one case of septic shock.

[3] Estimated based on post-marketing data

[4] Vaccination complications were related to the mandatory vaccinations.

Description of specific adverse reactions in patients with PNH

Infections

Based on its mechanism of action, the use of pegcetacoplan may potentially increase the risk of infections, particularly infections caused by encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* (see *Warnings and precautions*). No serious infection caused by encapsulated bacteria was reported during Study APL2302. Forty-eight patients experienced an infection during the study. 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. Eleven patients experienced an infection during study APL2-308. All but one infection were reported as mild or moderate in intensity. One patient who had an infection developed septic shock and died.

Haemolysis

Nineteen patients treated with pegcetacoplan during Study APL2-302 reported haemolysis. 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 cases of haemolysis during study APL2-308

in patients treated with pegcetacoplan. None of these cases were reported as serious or led to discontinuation of pegcetacoplan. The dose of pegcetacoplan was increased in all 3 patients.

Injection site reactions

Injections site reactions (e.g. erythema, swelling, pruritus, and pain) have been reported during Studies APL2-302.These reactions were mild to moderate in intensity and did not lead to discontinuation of treatment.

Diarrhoea

Cases of diarrhoea have been reported during Studies APL2-302, none of them were severe or led to discontinuation of treatment.

Immunogenicity

The immunogenicity of Aspaveli was assessed using specific anti-drug antibody (ADA) tests, one specific for the detection of ADAs against the peptide component of pegcetacoplan (anti-pegcetacoplan peptide) and a second specific for ADAs against the polyethylene glycol (PEG) component of pegcetacoplan (anti-PEG).

Anti-drug antibody incidence (treatment-emergent ADAs or elevated ADA levels) 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.

C3G and primary IC-MPGN

Summary of the safety profile

The most-commonly reported adverse drug reactions in patients with C3G or primary IC-MPGN treated with pegcetacoplan were infusion site reactions.

Tabulated list of adverse reactions

Table 2 gives the adverse reactions observed from the clinical studies with pegcetacoplan in patients with C3G or primary IC-MPGN.

Adverse reactions are listed by MedDRA 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 2: Adverse reactions in patients with C3G or primary IC-MPGN from clinical trials APL2-C3G-310, APL2-C3G-314, APL2-201 and APL2-C3G-204

System Organ Class	Frequency	Adverse reaction
Gastrointestinal disorders	Very common	Nausea
Skin and subcutaneous tissue disorders	Common	Pruritus (non-infusion site)
Musculoskeletal and connective tissue disorders	Common	Arthralgia
General disorders and administration site conditions	Very common	Pyrexia Infusion site reactions* (pain, erythema, pruritus, swelling, induration)

*Include high level term (HLT) Infusion site reactions and HLT Injection site reactions.

Transplanted patients

In transplanted patients with C3G or primary IC-MPGN (N=5), included in Study APL2-C3G-310, the safety profile appeared consistent with the overall results.

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 reaction 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.

Immunogenicity

Two different assays for the detection of anti-pegcetacoplan peptide 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.

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.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of overdose have been reported.

Properties/Effects

ATC code

L04AJ03

Pegcetacoplan is a symmetrical molecule comprised of two identical pentadecapeptides covalently bound to the ends of a linear 40-kDa polyethylene glycol (PEG) molecule. The molecular weight of pegcetacoplan is 43.5 kilodalton (kDa). 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 drug product.

Mechanism of action

Pegcetacoplan binds to complement protein C3 and its activation fragment C3b with high affinity, thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation. In PNH, extravascular haemolysis (EVH) is facilitated by C3b opsonization 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 activation of C3, initiated by all (alternative, classical and lectin) complement pathways with excessive deposition of C3 breakdown products in the glomeruli of the kidney. This leads 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.

Pharmacodynamics

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.

At Week 26, the proportion of patients with an at least two-orders-of-magnitude reduction from baseline in C3c staining intensity on renal biopsy was 74.3% in the pegcetacoplan group, with 71.4% achieving a staining score of zero as compared to 11.8% of patients with a decrease by two orders of magnitude and 8.8% reaching a staining score of zero in the placebo group.

In Study APL2-C3G-204, in patients with post-transplant recurrent disease, the mean serum C3 concentration increased from 0.70 g/L at baseline to 2.80 g/L at Week 52, and the mean serum sC5b-9 concentration decreased from 525.4 ng/mL at baseline to 151.0 ng/mL at Week 52.

Cardiac Electrophysiology

No specific studies have been conducted to determine the potential for pegcetacoplan to delay cardiac repolarization. Pegcetacoplan is a PEGylated peptide structure and showed no inhibition in the human ether-a-go-go gene (hERG) ion channel assay. Analysis of concentration-QTc confirmed no effect on cardiac repolarisation (QT interval corrected for heart rate).

Clinical efficacy

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, randomized 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 subcutaneous twice weekly in addition to their current dose of eculizumab. Patients were then randomized 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 randomized controlled period (RCP). Randomization 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/µL; ≥100,000/µL). 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).

Patients were vaccinated against *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* Type B (Hib), either within 2 years prior to Day 1 or within 2 weeks after starting treatment with pegcetacoplan. Patients vaccinated after Day 1 of treatment received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. In addition, prophylactic antibiotic therapy was administered at the discretion of the investigator in accordance with local treatment guidelines for patients with PNH who are receiving treatment with a complement inhibitor. Pegcetacoplan was administered as a subcutaneous infusion; the infusion time was approximately 20 to 40 minutes.

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 recorded prior to taking the first dose of pegcetacoplan. 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 3*). 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 3: Patient Baseline Demographics and Characteristics in Study APL2-302

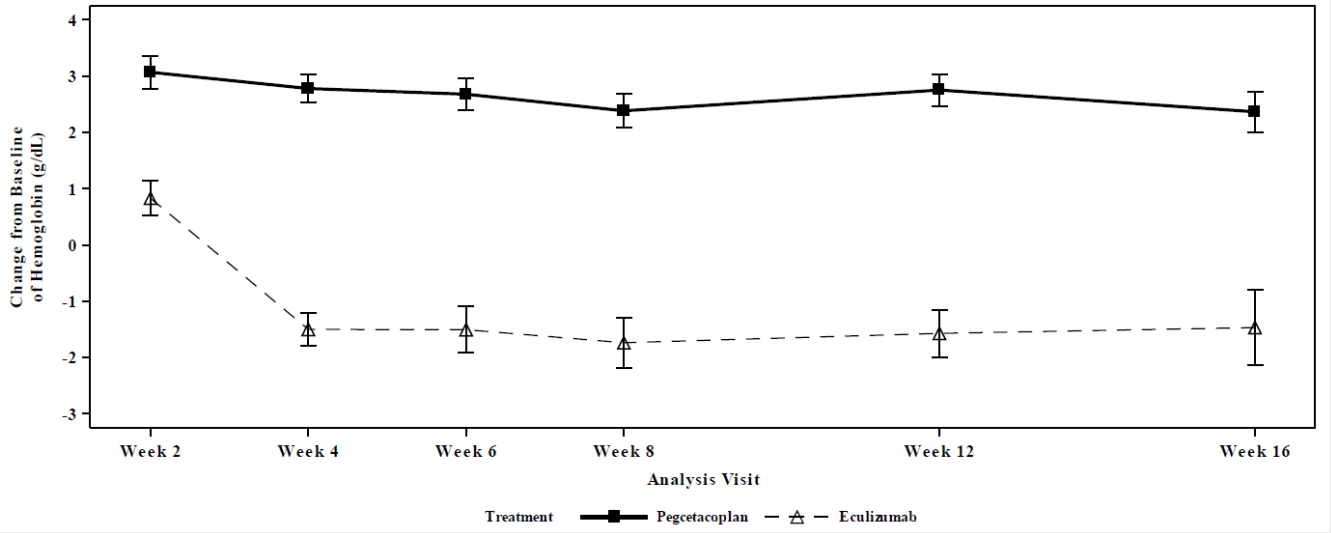
Parameter	**Statistics**	**Pegcetacoplan (n=41)**	**Eculizumab (n=39)**
Age (years)	Mean (SD)	50.2 (16.3)	47.3 (15.8)
Dose level of eculizumab at baseline Every 2 weeks i.v. 900 mg Every 11 days i.v. 900 mg Every 2 weeks i.v. 1200 mg Every 2 weeks i.v. 1500 mg	 n (%) n (%) n (%) n (%)	 26 (63.4) 1 (2.4) 12 (29.3) 2 (4.9)	 29 (74.4) 1 (2.6) 9 (23.1) 0
Women	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)
Hb level (g/dL)	Mean (SD)	8.7 (1.1)	8.7 (0.9)
ARC (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 score*	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).

The adjusted mean change from baseline in Hb level was 2.4 g/dL in the group treated with pegcetacoplan versus -1.5 g/dL in the eculizumab group, demonstrating an adjusted mean increase of 3.8 g/dL with pegcetacoplan compared to eculizumab at Week 16 (Figure 1).

Figure 1: LS Mean (± SE) Change from Baseline to Week 16 in Haemoglobin (g/dL) in APL2-302



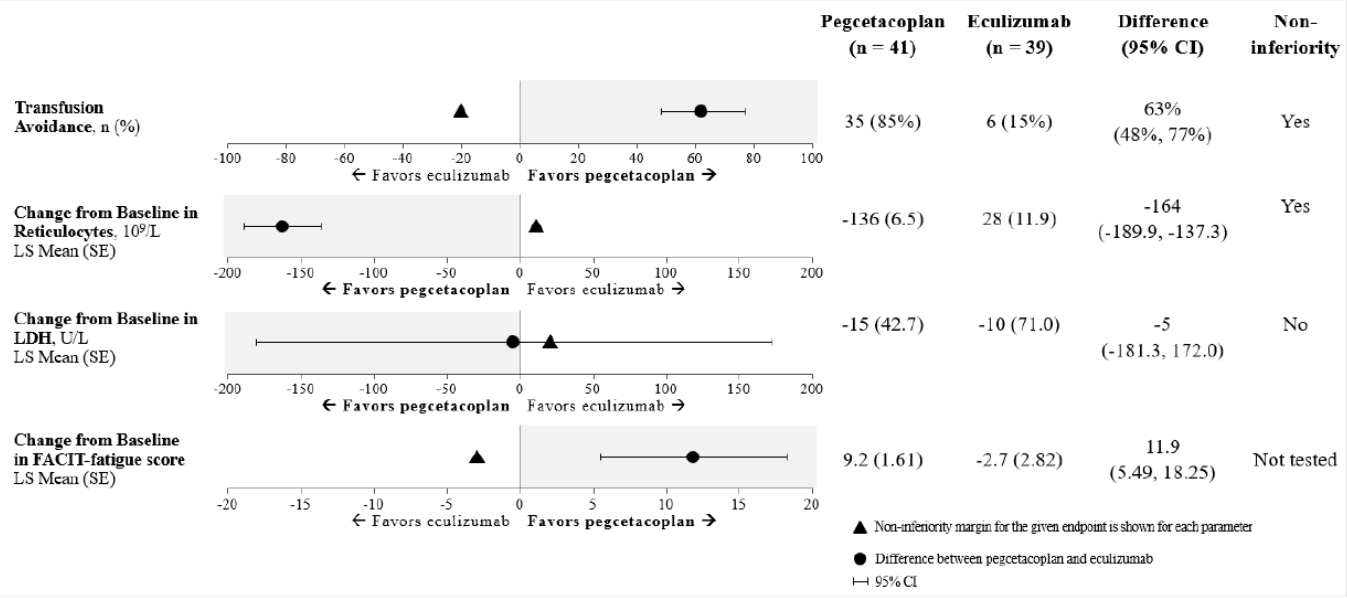
Non-inferiority was also demonstrated in key secondary endpoints of transfusion avoidance and ARC compared to baseline. Transfusion avoidance was achieved in 85% of patients in the group treated with pegcetacoplan, as compared to 15% in the eculizumab group.

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

Due to hierarchical testing, statistical testing for the change in FACIT-Fatigue score from baseline 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.

In patients treated with pegcetacoplan, primary and key secondary efficacy analyses showed no notable differences based on sex, race, or age.

Hb normalization was achieved in 34% of patients in the pegcetacoplan group versus 0% in the eculizumab group at Week 16. Normalization of ARC was achieved in 78% of patients in the group treated with pegcetacoplan versus 3% in the eculizumab group. LDH normalization 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.

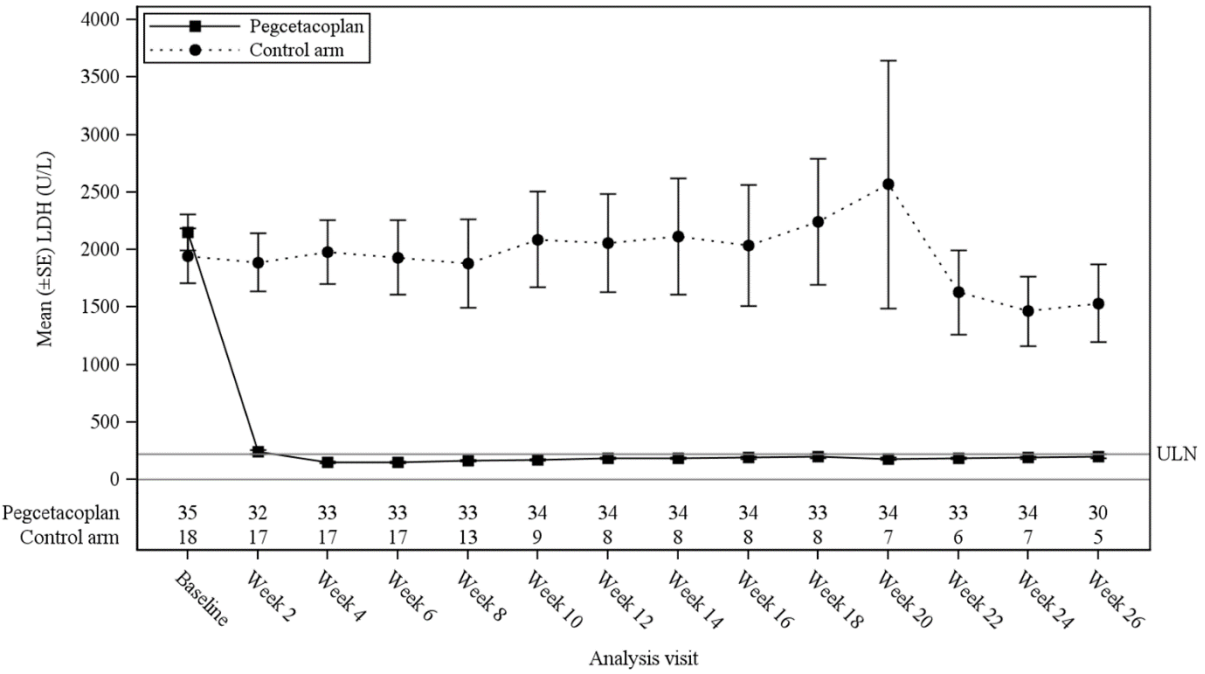
A total of 53 patients were randomised, 35 to pegcetacoplan and 18 patients to the control arm. Demographics and baseline disease characteristics were generally well balanced between treatment arms. The mean age was 42.2 years in the pegcetacoplan arm and 49.1 years in the control arm. The mean number 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 Hb response in the absence of transfusions, change in Hb level, and change in ARC, the group treated with pegcetacoplan demonstrated a significant treatment difference versus the control arm (Table 4).

Table 4: Key secondary endpoints: analysis in study APL2-308

Parameter	**Pegcetacoplan (N=35)**	**Control arm (N=18)**	**Difference (95% CI) p-value**
Hb 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 Hb 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] Hb 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 1 080 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 co-transporter-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 5). 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 5: Patient baseline demographics and disease characteristics in study APL2-C3G-310

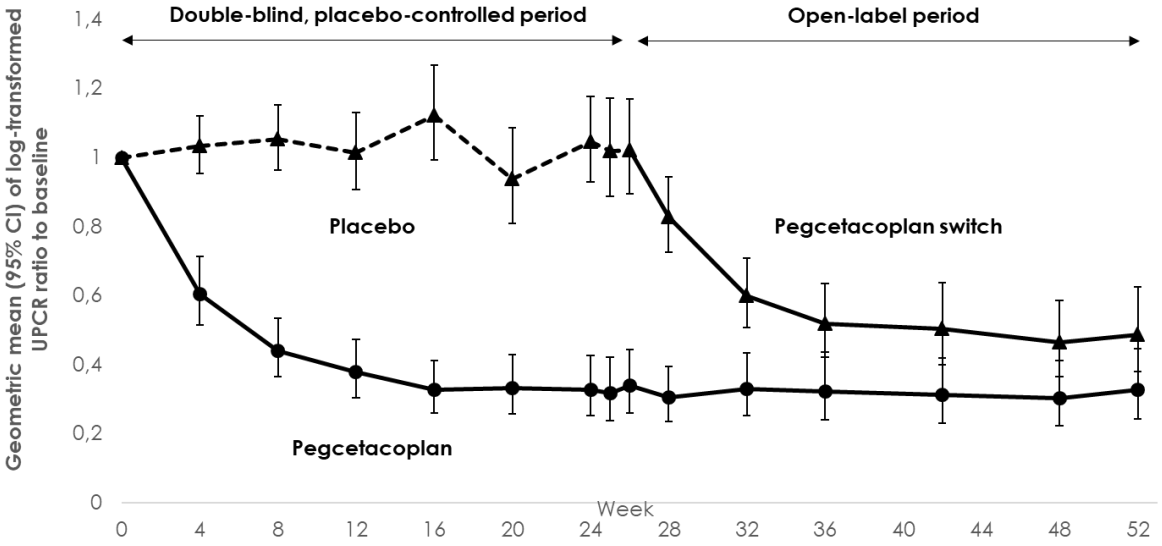
Parameter	Statistics	Pegcetacoplan (N=63)	Placebo (N=61)
Age (years)	Mean (SD)	28.2 (17.1)	23.6 (14.3)
Adolescents (12 – 17 years)	n (%)	28 (44.4)	27 (44.3)
Adults ≥18 years	n (%)	35 (55.6)	34 (55.7)

Parameter	Statistics	Pegcetacoplan (N=63)	Placebo (N=61)
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

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, with 60.3% of patients treated with pegcetacoplan achieving a ≥50% reduction in uPCR compared to 4.9% in the placebo group ($p < 0.0001$).

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 (nominal $p<0.0001$), indicating disease modification in pegcetacoplan treated patients.

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 (nominal $p=0.0333$). The effect of pegcetacoplan on eGFR was sustained through Week 52.

Efficacy of similar magnitude was observed for proteinuria reduction ≥50%, C3 staining clearance and eGFR stabilisation in all relevant subgroups 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.

Pharmacokinetics

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).

Steady-state serum concentrations following twice weekly dosing at 1080 mg in PNH patients 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 µg/mL (18.6%) and 706 µg/mL (15.1%) in patients treated for 16-weeks. 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. No formal absolute bioavailability study has been performed; a cross-study comparison of exposure following administration of SC and IV formulations in healthy volunteers estimated the bioavailability to be 87%.

Steady-state serum concentrations following twice weekly dosing at 1 080 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) central volume of distribution of pegcetacoplan is approximately 3.98 L (32%) in patients with PNH.

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.

Metabolism

Based on its PEGylated peptide structure, the degradation of pegcetacoplan is expected to occur via catabolic pathways into small peptides, amino acids and PEG.

Elimination

Following multiple subcutaneous dosing of pegcetacoplan, the estimated mean (CV%) of clearance (CL) is 0.015 L/h (30%) and median effective half-life of elimination ($t_{1/2}$) is 8.6 days in patients with PNH. Results of a radiolabelled study in cynomolgus monkeys suggest the primary route of elimination of the labelled peptide moiety is via urinary excretion.

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/Nonlinearity

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

Kinetics in specific patient groups

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

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 (see *Dosage/Administration*). 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 end-stage renal disease (ESRD) requiring dialysis.

Liver impairment

No specific studies have been conducted to determine the effect of hepatic impairment on the pharmacokinetics of pegcetacoplan. As biotransformation is mainly via catabolism, hepatic impairment is not expected to influence the clearance of pegcetacoplan (see *Patients with hepatic disorders*).

Elderly population

Based on population pharmacokinetic analysis, the apparent clearance (CL/F) in elderly patients and patients less than 65 years of age was similar and no apparent age-related differences were observed (see *Dosage/Administration - Elderly patients*). The number of elderly patients was however limited.

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 *Dosage/Administration*. The model-predicted exposure for adolescents with C3G or primary IC-MPGN is adequately matched to the adult reference exposure.

Preclinical 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.

Repeated dose toxicity

Repeat-dose studies in rabbits and cynomolgus monkeys with daily subcutaneous doses of pegcetacoplan up to 7 times the human dose (1080 mg twice weekly) were conducted. 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.

Renal tubular degeneration was observed microscopically in both species at exposures (Cmax 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.

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.

Carcinogenicity

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

Reproductive Toxicity

Reproductive animal studies were conducted in cynomolgus monkeys. Pegcetacoplan treatment of pregnant cynomolgus monkeys at a subcutaneous dose of 28 mg/kg/day (2.9 times the human steady-state Cmax) from the gestation period through parturition resulted in a statistically significant increase in abortions (31.6%) or stillbirths (21.1%) compared to controls (5.0% and 0%, respectively).

The increases were considered pegcetacoplan-related and adverse. Based on the increased incidence of abortions and stillbirths at 28 mg/kg/day, the NOAEL in this study was established at 7 mg/kg/day.

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).

Fertility

Specific rodent studies of fertility and early embryonic development with pegcetacoplan have not been conducted because pegcetacoplan is pharmacologically active only in humans and nonhuman primates. Microscopically examined male and female sex organs in the repeat-dose toxicity studies in monkeys showed no adverse effects of pegcetacoplan in males or females.

Lactation

Less than 1% pegcetacoplan excretion in milk has been demonstrated in monkeys; therefore, the probability of clinically relevant exposure of breastfed infant through breastmilk is considered minimal.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Store in the refrigerator (2-8°C).

Keep the container in the outer carton in order to protect the contents from light.

Keep out of the reach of children.

Instructions for handling

Detailed information preparation and for administration of Aspaveli are provided in the package leaflet.

Do not use if the liquid looks cloudy, contains particles, or is dark yellow.

Dispose of partially used vials and single use items in accordance with local requirements.

Authorisation number

68674

Packs

Aspaveli is presented as ready-to-use solution in one-way vials.

1 vial [A]

8 vials [A]

Marketing authorisation holder

Swedish Orphan Biovitrum AG, Basel

Date of revision of the text

October 2025