swissmedic

Date: 4 April 2025
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):	1080 mg
Route(s) of administration:	subcutaneous use
Marketing authorisation holder:	Swedish Orphan Biovitrum AG
Marketing authorisation no.:	68674
Decision and decision date:	approved on 3 February 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

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
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
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
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PNH	Paroxysmal nocturnal haemoglobinuria
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
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)

2 Background information on the procedure

2.1 Applicant's request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 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 6 January 2022.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Aspaveli is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH), who have haemolytic anaemia (see *Clinical efficacy*).

2.2.2 Approved indication

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*).

2.2.3 Requested dosage

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	28 May 2024
Formal control completed	26 June 2024
Preliminary decision	24 October 2024
Response to preliminary decision	15 December 2024
Final decision	3 February 2025
Decision	approval

Swissmedic has not assessed the primary data (e.g. study reports) submitted with this application and relies for its decision on the assessment of the foreign reference authority, the European Medicines Agency (EMA). This SwissPAR relates to the publicly available assessment report Aspaveli, EMEA/H/C/005553/II/0011, issued by the EMA.

3 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the European Medicines Agency (EMA). The nonclinical aspects in this SwissPAR refer to the publicly available assessment report Aspaveli, EMEA/H/C/005553/II/0011, issued by the EMA.

4 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the European Medicines Agency (EMA). The clinical aspects in this SwissPAR refer to the publicly available assessment report Aspaveli, EMEA/H/C/005553/II/0011, issued by the EMA.

5 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.

6 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Aspaveli, solution for infusion 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. 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*).

Dosage/Administration

Aspaveli is for subcutaneous infusion.
Therapy must be initiated under the supervision of a healthcare professional experienced in the management of patients with haematological 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 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.
Paroxysmal nocturnal haemoglobinuria (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*).

Usual dosage

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

Change from C5-inhibitors to Aspaveli

- 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

- 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.

Delayed administration

If a dose of Aspaveli is missed, it should be administered as soon as possible, and then treatment should be resumed with the regular schedule.

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 haemodialysis (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.

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*.

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, 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

Summary of the safety profile

The most commonly reported adverse reactions in patients 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 with pegcetacoplan in patients with PNH. 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 drug reactions

System Organ Class	**Frequency**	**Adverse reaction**
Infections and infestations	Very common	Upper respiratory tract infection Urinary tract infection
	Common	Sepsis[1] 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
Metabolism and nutrition disorders	Common	Hypokalaemia
Nervous system disorders	Very common	Headache Dizziness
Vascular disorders	Common	Hypertension
	Very common	Cough

System Organ Class	Frequency	Adverse reaction
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea Epistaxis Oropharyngeal pain Nasal congestion
Gastrointestinal disorders	Very common	Abdominal pain Diarrhoea
	Common	Nausea
Skin and subcutaneous tissue disorders	Common	Erythema Rash
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

System Organ Class	Frequency	Adverse reaction
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
Hepatobiliary disorders	Common	Alanine aminotransferase increased Bilirubin increased
Injury, poisoning and procedural complications	Very common	Vaccination complication[2]

The adverse reactions listed in the table are from clinical studies APL2-302, APL2-308, Study 202, Study 204, and Study CP0514 in PNH.

Medically similar terms are grouped, where appropriate, on the basis of similar medical concept.

[1] Sepsis includes one case of septic shock.

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

Description of specific adverse reactions

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 reported haemolysis during Study APL2-302 in 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 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, pruritis, 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 antibodies (ADA), 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 (seroconverted 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 seroconversions and 9 were treatment-boosted.

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 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.

Pharmacodynamics

In Study APL2-302, the mean 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 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.
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

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 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.

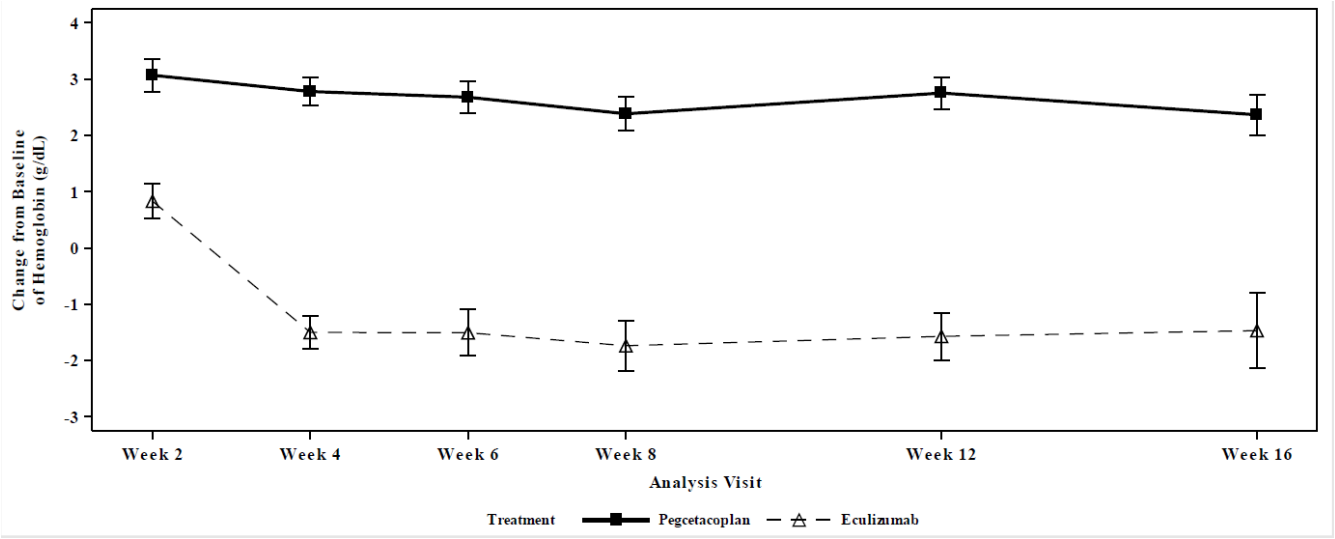
The primary and secondary efficacy endpoints were assessed at Week 16. The primary efficacy endpoint was change from baseline to Week 16 (during RCP) in haemoglobin level. Baseline was defined as the average of measurements recorded prior to taking the first dose of pegcetacoplan. Key secondary efficacy 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 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)
Dose level of eculizumab at baseline Every 2 weeks IV 900 mg Every 11 days IV 900 mg Every 2 weeks IV 1200 mg Every 2 weeks IV 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)
Haemoglobin level (g/dL)	Mean (SD)	8.7 (1.1)	8.7 (0.9)
Absolute 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 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)

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



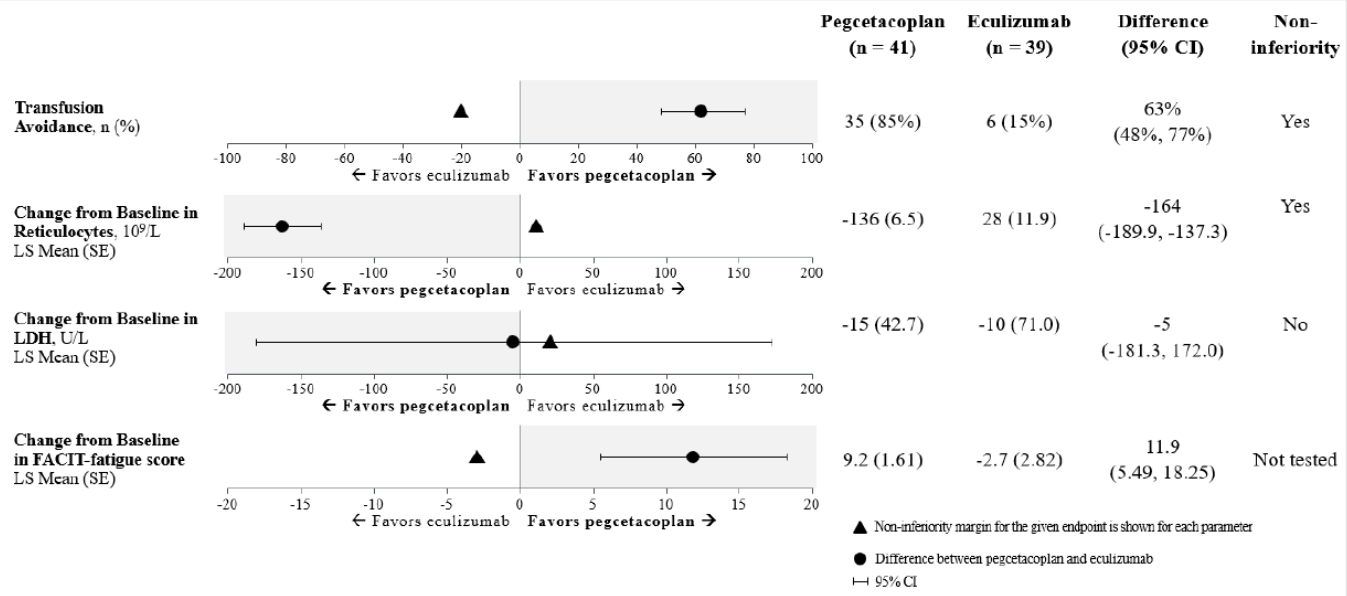
Non-inferiority was also demonstrated in key secondary endpoints of transfusion avoidance and ARC compared to baseline. Transfusion avoidance was achieved in 85% of patients in the group treated with pegcetacoplan, as compared to 15% in the eculizumab group.

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.

Haemoglobin 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 haemoglobin 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 packed red blood cell (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 haemoglobin 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.

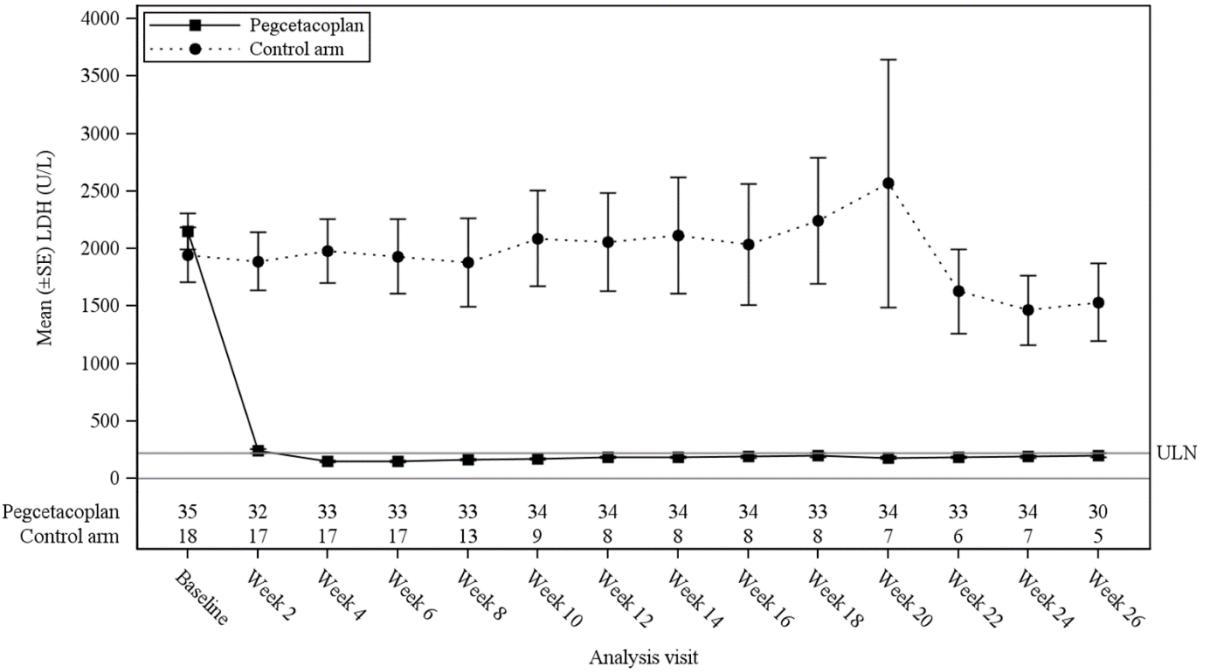
A total of 53 patients were randomised, 35 to pegcetacoplan and 18 patients to the control arm. Demographics and baseline disease characteristics were generally well balanced between treatment arms. The mean age was 42.2 years in the pegcetacoplan arm and 49.1 years in the control arm. The mean number 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 haemoglobin 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 haemoglobin 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 haemoglobin stabilisation, defined as avoidance of a >1 g/dL decrease in haemoglobin 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 haemoglobin 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

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%.

Distribution

The mean (%CV) central volume of distribution of pegcetacoplan is approximately 3.98 l (32%) in patients with PNH.

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. Results of a radiolabelled study in cynomolgus monkeys suggest the primary route of elimination of the labelled peptide moiety is via urinary excretion.

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.

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, race or sex based on the results of population PK analysis.

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. 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 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. There are no available clinical data for the use of pegcetacoplan in patients with ESRD requiring haemodialysis.

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 section *Elderly patients*). The number of elderly patients was however limited.

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 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

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