1. NAME OF THE MEDICINAL PRODUCT

ASPAVELI

Patient safety information card

The marketing of ASPAVELI is subject to a risk management plan (RMP) including a `Patient safety information card`. The `Patient safety information card` emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the card before starting treatment.

Prescriber guide

This Product is marketed with prescriber guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 mL vial contains 1,080 mg of pegcetacoplan.
Each mL contains 54 mg of pegcetacoplan.

Excipients with known effect
Each mL contains 41 mg of sorbitol.
Each vial contains 820 mg of sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

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

Pegcetacoplan is administered twice weekly as a 1,080 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.

PNH is a chronic disease and treatment with ASPAVELI is recommended to continue for the patient's lifetime, unless the discontinuation of this medicinal product is clinically indicated (see section 4.4).

Patients switching to ASPAVELI from a C5 inhibitor
For the first 4 weeks, pegcetacoplan is administered as twice weekly subcutaneous doses of 1,080 mg in addition to the patient's current dose of C5 inhibitor treatment to minimise the risk of haemolysis with abrupt treatment discontinuation. After 4 weeks, the patient should discontinue C5 inhibitor before continuing on monotherapy with 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 section 5.2).

Dose adjustment
The dosing regimen may be changed to 1,080 mg every third day (e.g., Day 1, Day 4, Day 7, Day 10, Day 13, and so forth) if a patient has a lactate dehydrogenase (LDH) level greater than 2 x upper limit of normal (ULN). In the event of a dose increase, LDH should be monitored twice weekly for at least 4 weeks (see section 4.4).

Missed dose
If a dose of pegcetacoplan is missed, it should be administered as soon as possible, then the regular schedule should be resumed.

Special populations

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

Renal impairment
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 section 5.2).

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

Paediatric population
The safety and efficacy of ASPAVELI in children with PNH aged 0 to <18 years have not yet been established. No data are available.
This medicinal product should not be used in children <12 years of age, as non-clinical safety data are not available for this age group.

Method of administration

ASPAVELI should only be administered via subcutaneous administration using a commercially available syringe system infusion pump. This medicinal product can be self-administered. When self-administration is initiated, the patient will be instructed by a qualified healthcare professional in

infusion techniques, the use of a syringe system infusion pump, the keeping of a treatment record, the recognition of possible adverse reactions, and measures to be taken in case these occur.

ASPAVELI should be infused in the abdomen, thighs, hips or upper arms. Infusion sites should be at least 7.5 cm apart from each other. The infusion sites should be rotated between administrations. Infusion into areas where the skin is tender, bruised, red, or hard should be avoided. Infusion into tattoos, scars, or stretch marks should be avoided. The 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 this medicinal product into the syringe. Administration should be completed within 2 hours after preparing the syringe. For instructions on the preparation and infusion of the medicinal product, see section 6.6.

4.3 Contraindications

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

Pegcetacoplan therapy must not be initiated in patients:

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

4.4 Special warnings and precautions for use

Serious infections caused by encapsulated bacteria

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

Patients with known history of vaccination

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

Patients without known history of vaccination

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

Monitoring patients for serious infections

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

Hypersensitivity

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

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

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

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

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

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

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

Excipients with known effect
Sorbitol content
ASPAVELI 1,080 mg contains 820 mg sorbitol in each vial.
Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

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

Pregnancy
There are no or limited amount of data from the use of pegcetacoplan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

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

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
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 and postmarketing experience with pegcetacoplan in patients with PNH. Adverse reactions are listed by MedDRA system organ class (SOC) and frequency, using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100) or rare (≥1/10 000 to <1/1 000), very rare (<1/10 000), and not known (cannot be estimated from available data).

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

Table 1: Adverse reactions from clinical trials[1] and postmarketing experience

MedDRA 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
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
Skin and subcutaneous tissue disorders	Common	Erythema Rash Urticaria[3]
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

MedDRA 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
Investigations	Common	Alanine aminotransferase increased Bilirubin increased
Injury, poisoning and procedural complications	Very common	Vaccination complication[4]

[1]Studies APL2-308, APL2-302, APL2-202, APL2-CP-PNH-204, and APL-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 from both clinical trial and postmarketing experience.
[4]Vaccination complications were related to the mandatory vaccinations.

Description of selected 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 section 4.4). No serious infection caused by encapsulated bacteria was reported during Study APL2-302. 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 non-serious, 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.

Immunogenicity

Anti-drug antibody (ADA) incidence (seroconverted ADA or boosted ADA from pre-existing level) were 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 of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

No case of overdose has been reported to date. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

Pharmacodynamic effects
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.

Clinical efficacy and safety
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 1,080 mg twice weekly. If required, the dose could be adjusted to 1,080 mg every 3 days.

Study in complement inhibitor-experienced adult patients (APL2-302)
Study APL2-302 was an open-label, randomised study with an active comparator-controlled period of 16 weeks followed by a 32-week open label period (OLP). This study enrolled patients with PNH who had been treated with a stable dose of eculizumab for at least the previous 3 months and with haemoglobin levels <10.5 g/dL.

Eligible patients entered a 4-week run-in period during which they received pegcetacoplan 1,080 mg subcutaneously twice weekly in addition to their current dose of eculizumab. Patients were then randomised in a 1:1 ratio to receive either 1,080 mg of pegcetacoplan twice weekly or their current dose of eculizumab through the duration of the 16-week randomised controlled period (RCP). Randomisation was stratified based on the number of packed red blood cell (PRBC) transfusions within the 12 months prior to Day -28 (<4; ≥4) and platelet count at screening (<100 000/mm^3; ≥100 000/mm^3). Patients who completed the RCP entered the OLP during which all patients received pegcetacoplan for up to 32 weeks (patients who received eculizumab during the RCP entered a 4-week run-in period before switching to pegcetacoplan monotherapy).

The primary and secondary efficacy endpoints were assessed at Week 16. The primary efficacy endpoint was change from baseline to Week 16 (during RCP) in haemoglobin level. Baseline was defined as the average of measurements prior to the first dose of pegcetacoplan (at the beginning of the run-in period). Key secondary efficacy endpoints were transfusion avoidance, defined as the proportion of patients who did not require a transfusion during the RCP, and change from baseline to Week 16 in absolute reticulocyte count (ARC), LDH level, and 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 1,080 mg every 3 days. Twelve patients were evaluated for benefit and 8 of the 12 patients demonstrated benefit from the dose adjustment.

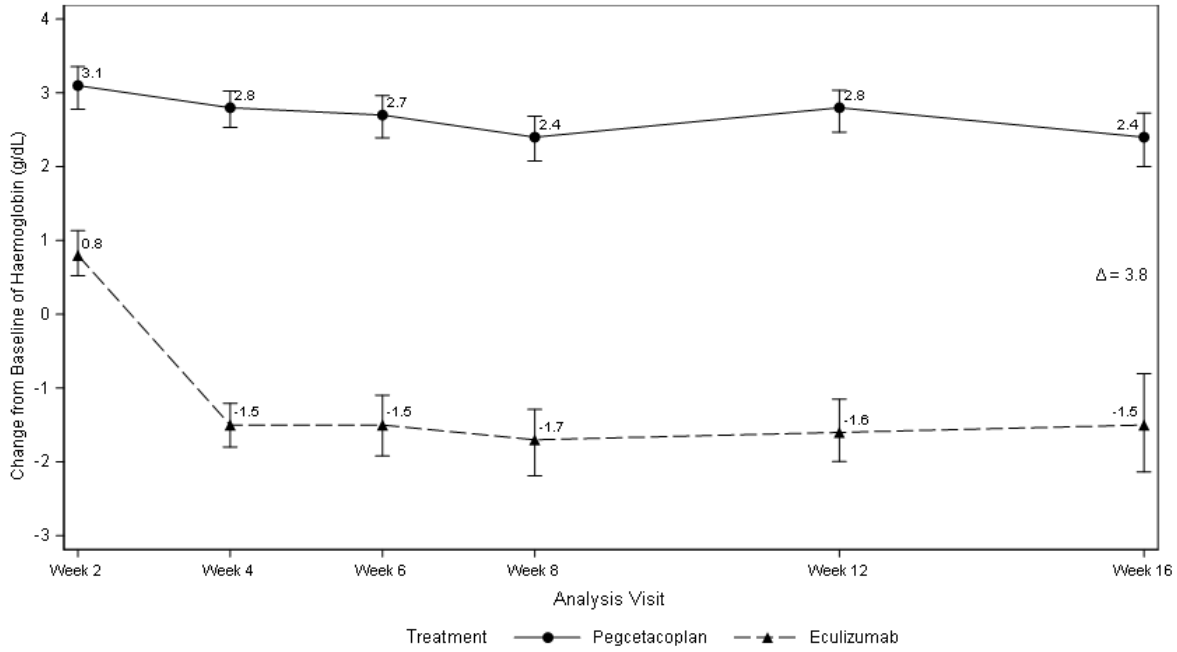
Table 2: Patient baseline demographics and characteristics in Study APL2-302

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

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

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

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



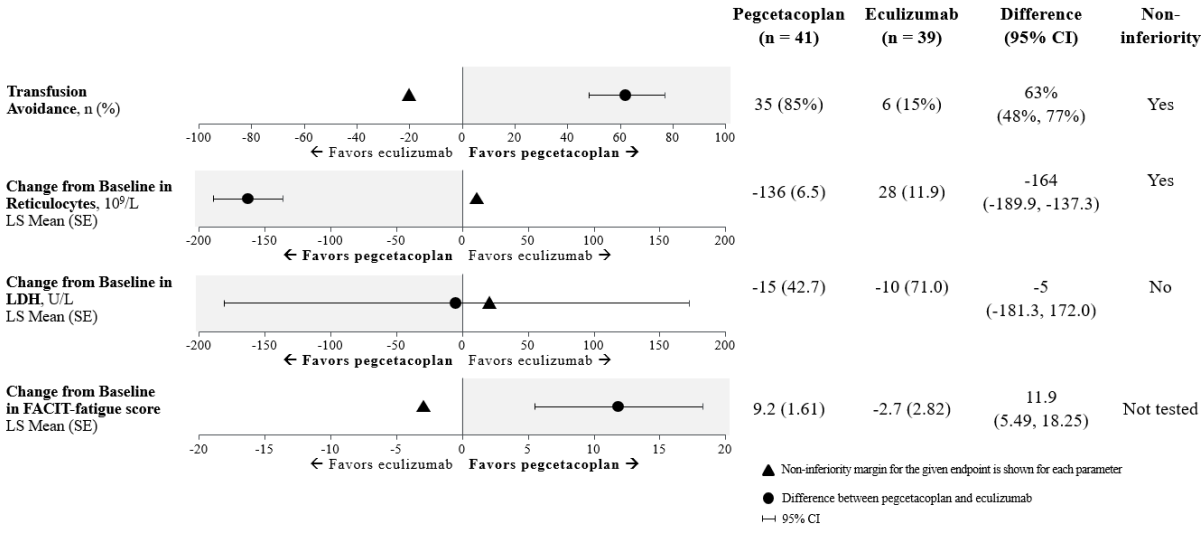
Non-inferiority was demonstrated in key secondary endpoints of transfusion avoidance and change from baseline in ARC.

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

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

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

Figure 2. Key secondary endpoints analysis in APL2-302



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

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

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

Study in complement inhibitor-naïve adult patients (APL2-308)
Study APL2-308 was an open-label, randomised, controlled study that enrolled patients with PNH who had not been treated with any complement inhibitor within 3 months prior to enrolment and with 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.

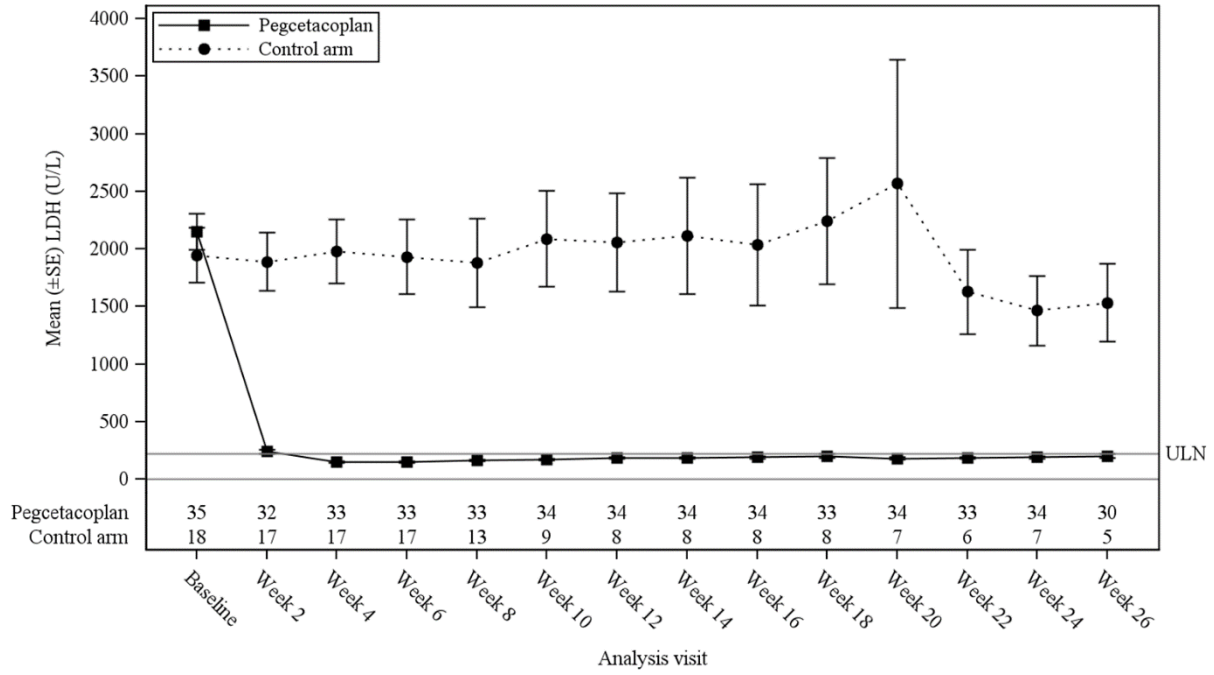
A total of 53 patients were randomised, 35 to pegcetacoplan and 18 patients to the control arm. Demographics and baseline disease characteristics were generally well balanced between treatment arms. The mean age was 42.2 years in the pegcetacoplan arm and 49.1 years in the control arm. The mean number 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

5.2 Pharmacokinetic properties

Absorption
Pegcetacoplan is administered by subcutaneous infusion and gradually absorbed into the systemic circulation with a median T_{max} between 108 and 144 hours (4.5 to 6.0 days) following a single subcutaneous dose to healthy volunteers. Steady-state serum concentrations following twice weekly dosing at 1,080 mg in patients with PNH were achieved approximately 4 to 6 weeks following the first dose. In complement inhibitor-experienced patients (Study APL2-302) the geometric mean (%CV) steady-state serum concentrations ranged between 655 (18.6%) and 706 (15.1%) µg/mL in patients treated for 16 weeks. Steady-state concentrations in the patients (n=22) that continued to receive pegcetacoplan up to Week 48 were 623 µg/mL (39.7%), indicating sustainable therapeutic concentrations of pegcetacoplan through Week 48. In complement inhibitor-naïve patients (Study APL2-308) the geometric mean (%CV) steady-state serum concentration at Week 26 was 744 µg/mL

(25.5%) with twice weekly dosing. The bioavailability of a subcutaneous dose of pegcetacoplan is estimated to be 76% based on population PK analysis.

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

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

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

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

Linearity/non-linearity
Exposure of pegcetacoplan increases in a dose proportional manner from 45 to 1,440 mg.

Special populations
No impact on the pharmacokinetics of pegcetacoplan was identified with age (19-81 years), 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 a 45% higher average concentration. Minimal data are available on the safety profile of pegcetacoplan for patients with a body weight below 50 kg.

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

Renal impairment
In a study of 8 patients with severe renal impairment, defined as creatinine clearance (CrCl) less than 30 mL/min using the Cockcroft-Gault formula (with 4 patients with values less than 20 mL/min), renal impairment had no effect on the pharmacokinetics of a single 270-mg dose of pegcetacoplan. There are minimal data on patients with PNH with renal impairment who have been administered the clinical dose of 1,080 mg twice weekly. There are no available clinical data for the use of pegcetacoplan in patients with ESRD requiring haemodialysis. See section 4.2.

5.3 Preclinical safety data

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

Animal reproduction
Pegcetacoplan treatment of pregnant cynomolgus monkeys at a subcutaneous dose of 28 mg/kg/day (2.9 times the human steady-state C_{max}) from the gestation period through parturition resulted in a statistically significant increase in abortions or stillbirths. No maternal toxicity or teratogenic effects

were observed in offspring delivered at term. Additionally, no developmental effects were observed in infants up to 6 months postpartum. Systemic exposure to pegcetacoplan was detected in foetuses from monkeys treated with 28 mg/kg/day from the period of organogenesis through the second trimester, but the exposure was minimal (less than 1%, not pharmacologically significant).

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

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

Animal toxicology
Repeat-dose studies were conducted in rabbits and cynomolgus monkeys with daily subcutaneous doses of pegcetacoplan up to 7 times the human dose (1,080 mg twice weekly). Histologic findings in both species included dose-dependent epithelial vacuolation and infiltrates of vacuolated macrophages in multiple tissues. These findings have been associated with large cumulative doses of long-chain PEG in other marketed PEGylated drugs, were without clinical consequence, and were not considered adverse. Reversibility was not demonstrated in the pegcetacoplan animal studies after one month and was not evaluated for a longer duration. Data from literature suggest reversibility of PEG vacuoles.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol
Sodium acetate trihydrate
Glacial acetic acid
Sodium hydroxide
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

A Type I glass vial with a stopper (cholorobutyl), and a seal (aluminium) with a flip-off cap (polypropylene) containing 54 mg pegcetacoplan/1 mL of sterile solution.

Each single pack contains 1 vial.

Multipack containing 8 (8 packs of 1) vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

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

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

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

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

Option 2: If transfer is done using a transfer needle and a syringe, follow the instructions below:
- Attach a sterile transfer needle to a sterile syringe.
- Pull back the plunger to fill the syringe with air, which should be about 20 mL.
- Make sure the vial is in upright position. Do not turn the vial upside down.
- Push the air-filled syringe with transfer needle attached through the centre of the vial stopper.
- The tip of the transfer needle should not be in the solution to avoid creating bubbles.
- Gently push the air from the syringe into the vial. This will inject the air from the syringe into the vial.
- Invert the vial.
- With the transfer needle tip in the solution, slowly pull the plunger to fill the syringe with all the liquid.
- Remove the filled syringe and the transfer needle from the vial.
- Do not recap the transfer needle. Unscrew the needle and throw it away in the sharps container.

Follow the device manufacturer’s instructions to prepare the infusion pump and tubing.

Potential areas for infusion include the abdomen, thighs, hips, or upper arms. Rotate infusion sites from one infusion to the next. If there are multiple infusion sites, they should be at least 7.5 cm apart.

The typical infusion time is approximately 30 minutes (if using two sites) or approximately 60 minutes (if using one site).

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

7. MANUFACTURER

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

8. REGISTRATION HOLDER

TrueMed Ltd.,
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P.O.B 8105, Netanya 4250499

9. REGISTRATION NUMBER

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