Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Pegcetacoplan

Proprietary Product Name: Empaveli

Sponsor: Apellis Australia Pty Ltd

August 2022

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
AH50/AP50	Alternative complement pathway haemolytic activity assay
ASA	Australia specific annex
ARC	Absolute reticulocyte count
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the concentration-time curve
C3	Complement component 3
C5	Complement component 5
$C_{avg,ss}$	Average concentration during a dosing interval at steady state
CH50	Classical complement pathway haemolytic activity assay
CI	Confidence interval
CL/F	Apparent clearance
$C_{max,ss}$	Maximum concentration at steady state
CMI	Consumer Medicines Information
COVID-19	Coronavirus disease 2019
CYP450	Cytochrome P450
CV	Coefficient of variation
DLP	Data lock point
DNA	Deoxyribonucleic acid
EC_{50}	Half maximal (50%) effective concentration
EMA	European Medicines Agency (European Union)
E_{max}	Maximal effect
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy

Abbreviation	Meaning
FDA	Food and Drug Administration (United States of America)
GVP	Good Pharmacovigilance Practices
IPIG	International Paroxysmal nocturnal haemoglobinuria Interest Group
Ig	Immunoglobulin
ITT	Intention-to-treat
LASA	Linear Analog Scale Assessment
LDH	Lactate dehydrogenase
LSM	Least square mean
mITT	Modified intention-to-treat
NOAEL	No observable effect levels
PASS	Post-authorisation safety study
PD	Pharmacodynamic(s)
PEG	Polyethylene glycol
PI	Product Information
PID	Pelvic inflammatory disease
PK	Pharmacokinetic(s)
PNH	Paroxysmal nocturnal haemoglobinuria
PopPK	Population pharmacokinetic(s)
PSUR	Periodic safety update report
QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Scale
QTc	Corrected QT interval
RMP	Risk management plan
SAE	Serious adverse event
SD	Standard deviation
Sobi	Swedish Orphan Biovitrum

Abbreviation	Meaning
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
T_{max}	Time of maximum concentration
RBC	Red blood cell
ULN	Upper limit of normal
US(A)	United States (of America)

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Product name:	Empaveli
Active ingredient:	Pegcetacoplan
Decision:	Approved
Date of decision:	28 January 2022
Date of entry onto ARTG:	3 February 2022
ARTG number:	346216
, *Black Triangle Scheme:*[1]	Yes. This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	Apellis Australia Pty Ltd;[2] Level 1, 718 High Street Kew East, VIC 3102
Dose form:	Solution for injection
Strength:	1080 mg/20 mL
Container:	Vial
Pack sizes:	One vial; and 8 vials
Approved therapeutic use:	*Empaveli is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have an inadequate response to, or are intolerant of, a C5 inhibitor.*
Route of administration:	Subcutaneous
Dosage:	*Before receiving treatment with Empaveli* For patient with known history of vaccination, ensure that patients have received vaccines against encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis* serogroups A, C, W, Y, and B, and Haemophilus influenzae type B

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.
[2] Sponsorship has been transferred to Swedish Orphan Biovitrum Pty Ltd post approval.
Current sponsor's address at the time of AusPAR publication: Floor 22, 44 Market Street, Sydney NSW 2000

within 2 years prior to starting Empaveli. For patient without known history of vaccination, administer required vaccines at least 2 weeks prior to receiving the first dose of Empaveli. If immediate therapy with Empaveli is indicated, administer required vaccines as soon as possible and provide patients with antibacterial drug prophylaxis until 2 weeks after vaccination (see Section 4.4 Special warnings and precautions for use of the Product Information).

Adult patients with paroxysmal nocturnal hemoglobinuria

Empaveli 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 (see method of administration and instructions for use of the Product Information).

Patients switching to Empaveli from a complement component 5 inhibitor (eculizumab rmc, ravulizumab rch)

For the first 4 weeks, Empaveli is administered as twice weekly subcutaneous doses of 1,080 mg in addition to the patient's current dose of complement component 5 (C5) inhibitor treatment to minimise the risk of haemolysis with abrupt treatment discontinuation. After 4 weeks, the patient should discontinue treatment with the C5 inhibitor before continuing monotherapy with Empaveli.

Dosage is also based on the lactate dehydrogenase level of the patient.

For further information refer to the Product Information.

Pregnancy category: B3

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Apellis Australia Pty Ltd;[2] (the sponsor) to register Empaveli (pegcetacoplan) 1080 mg/20 mL, solution for injection for the following proposed indication:

Treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH).

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare, chronic, acquired, potentially life threatening, haematologic disease characterised by debilitating complement mediated haemolytic anaemia, as well as bone marrow failure, increased risk of thrombosis and systemic complications of pulmonary, hepatic, renal, gastrointestinal, and neurological nature. Uncontrolled complement activation leads to intravascular haemolysis mediated by the complement component 5 (C5) dependent membrane attack complex and extravascular haemolysis mediated by accumulation of complement component 3 (C3) fragments on red blood cell (RBC) surfaces. The sponsor reported that almost 63% of the patients who had not yet initiated eculizumab had a history of bone marrow failure, and about 53% had a history of aplastic or hypoplastic anaemia. The proportion of patients with bone marrow failure was highest in those with the smaller clone size (89.2% of patients with a clone > 10%), and lowest in those with the larger clone size (46.0% of patients with a clone > 50%).[3] In addition to bone marrow failure, other bone marrow disorders, including myelodysplastic syndromes, myelofibrosis, and/or acute myeloid leukaemia have been reported before or after diagnosis with PNH.[1,4,5,6]

Bone marrow transplantation and complement inhibitor therapies are the only effective therapies for the treatment of PNH. The only potentially curative therapy for PNH is allogeneic bone marrow transplantation. However, this procedure is associated with substantial morbidity and mortality. While bone marrow function may be restored in up to half of patients receiving a transplant, the sponsor comments that considerable challenges and risks (for example, graft failure and infection) reserve this option for patients with severe bone marrow failure, reoccurring life threatening thromboembolic events, or refractory, transfusion dependent haemolytic anaemia.

Treatment options for PNH remained limited and often inadequate until eculizumab, a humanised monoclonal antibody targeting C5 of the complement cascade became available. Soliris (eculizumab)[7] received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 20 March 2009 for PNH to reduce haemolysis and for atypical haemolytic uraemic syndrome. On 1 July 2020, eculizumab was also entered on the ARTG for adult patients with neuromyelitis optica spectrum disorder who are anti-aquaporin 4 antibody positive.[8] On 17 October 2019, Ultomiris (ravulizumab),[9] a second humanised monoclonal antibody C5 inhibitor, was entered on the ARTG for the treatment of adult patients with PNH.[10]

Soliris (eculizumab) is a genetically engineered humanised monoclonal antibody directed against the α-chain of the C5 complement protein approved to the treatment of PNH in adults. The recommended eculizumab dosing regimen for the treatment of adult patients (18 years of age and older) with PNH consists of a 4-week initial phase (intravenous

[3] Schrezenmeier, H. et al. Baseline Clinical Characteristics and Disease Burden in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH): Updated Analysis from The International PNH Registry, *Ann Hematol*, 2020; 99(7): 1505-1514.
[4] Jang, J.H. et a. Predictive Factors of Mortality in Population of Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH): Results from a Korean PNH Registry, *J Korean Med Sci*, 2016; 31: 214-221.
[5] Schrezenmeier, H, et al. Baseline Characteristics and Disease Burden in Patients in the International Paroxysmal Nocturnal Hemoglobinuria Registry, *Haematologica*, 2014; 99(5): 922-929.
[6] Hill, A. et al. Eculizumab Prevents Intravascular Hemolysis in Patients with Paroxysmal Nocturnal Hemoglobinuria and Unmasks Low-Level Extravascular Hemolysis Occurring through C3 Opsonization, *Haematologica*, 2010; 95(4): 567-573.
[7] Soliris was first registered on the ARTG on 20 March 2009 (ARTG number: 138885).
[8] AusPAR for Soliris (eculizumab) extension of indication, published on 2 December 2020. Available at: https://www.tga.gov.au/auspar/auspar-eculizumab.
[9] Ultomiris was first registered on the ARTG on 17 October 2019 (ARTG number: 311926).
[10] AusPAR for Ultomiris (ravulizumab) new chemical entity, published on 13 December 2019. Available at: https://www.tga.gov.au/auspar/auspar-ravulizumab.

infusion every week for the first 4 weeks) followed by an intravenous infusion maintenance phase every 14 ± 2 days beginning on the fifth week of treatment.

Ultomiris (ravulizumab) is a long-acting humanised monoclonal immunoglobulin (Ig)G2/4K antibody produced in Chinese hamster ovary cell culture by recombinant deoxyribonucleic acid (DNA) technology. Ravulizumab is administered by intravenous infusion. The recommended ravulizumab dosing regimen for the treatment of adult patients (18 years of age and older) with PNH consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. Maintenance doses should be administered once every 8 weeks, starting 2 weeks after loading dose administration.

Eculizumab and ravulizumab are similar in that they are both humanised monoclonal antibodies that specifically bind to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. Consistent with this mechanism of action, they have both been shown to similarly control intravascular haemolysis monitored by lactate dehydrogenase (LDH) levels. Both eculizumab and ravulizumab are administered by intravenous infusion, but the frequency of administration is notably longer with ravulizumab (every 8 weeks) than with eculizumab (every 2 weeks).

The sponsor comments that although C5 inhibition controls intravascular haemolysis, it does not prevent extravascular haemolysis due to C3 fragment deposition on PNH red blood cells, but instead increases it, leading to further haemolysis. The presence of low haemoglobin levels, elevated reticulocyte counts and bilirubin levels, and continued need for transfusions, despite C5 inhibition and relatively well-controlled LDH levels, and persistent patient reported fatigue are indicators of ongoing disease activity. Therefore, the sponsor considers that there is significant remaining medical need for alternative treatment options for patients with PNH that can demonstrate significant benefit over existing current therapy with an acceptable safety profile. The sponsor states that pegcetacoplan was developed to address this remaining unmet medical need.

Regulatory status

This product is considered a new chemical entity or biosimilar medicine for Australian regulatory purposes.

At the time the TGA considered this application, a similar application had been approved in the United States of America (USA) on 14 May 2021. A similar application was under consideration in European Union (EU) (submitted on 9 September 2020).

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	9 September 2020	Under consideration	Under consideration
United States of America	14 September 2020	Approved on 14 May 2021	*Treatment of adult patients with paroxysmal nocturnal haemoglobinuria*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2020-05447-1-6

Description	Date
Designation (Orphan)[11]	4 September 2020
Submission dossier accepted and first round evaluation commenced	30 November 2020
First round evaluation completed	6 May 2021
Sponsor provides responses on questions raised in first round evaluation	5 July 2021
Second round evaluation completed	16 August 2021
Delegate's Overall benefit-risk assessment	28 December 2021
Sponsor's pre-Advisory Committee response	Not applicable

[11] 'Orphan drugs' are often developed to treat small and very specific patient populations who suffer from rare diseases and conditions. In order to facilitate orphan drug access to the Australian marketplace and help offset orphan drug development costs the TGA waives application and evaluation fees for prescription medicine registration applications if a related orphan designation is in force. A medicine may be eligible for orphan drug designation if all orphan criteria set by the TGA are met. The orphan designation application precedes the registration application and the designation is specific to the sponsor, orphan indication for which designation was granted and dosage form of the medicine.

Description	Date
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	28 January 2022
Completion of administrative activities and registration on the ARTG	3 February 2022
Number of working days from submission dossier acceptance to registration decision*	243

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Relevant guidelines or guidance documents referred to by the Delegate are listed below:

- European Medicines Evaluation Agency (EMEA), Committee for Proprietary Medicinal Products (CPMP), Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study, CPMP/EWP/2330/99, 31 May 2001.
- Clinical Investigation of Medicinal Products for Long-Term Use, 3CC6a, February 1987 (date of first adoption).

Quality

A summary of the findings of the quality evaluation is included in this section.

Pegcetacoplan is a complement protein C3 inhibitor.

The drug substance is fully synthetic. Its manufacture is sufficiently described in terms of steps, reactants and experimental conditions. The starting materials are isolated compounds and well-characterised, controlled with specifications and fate purge studies. Analytical methods used in the analysis are validated and appropriate. Final release and shelf-life specifications are considered appropriate to ensure drug substance quality.

The drug substance re-test period is 12 months when stored at –20°C in the proposed container closure system.

The drug product is a sterile solution for injection, packed in 20 mL type I clear glass vial chlorobutyl rubber stopper and aluminium seal with flip off disc in a carton, containing alternatively one or eight vials. Each vial is for single use and contains no antimicrobial preservative.

The product is primarily intended to be administered in a home setting by the patient or caregiver. It can also be administrated in a hospital, clinic setting, or a specialist's outpatient office by health care professionals. Administration is intended via commercially available delivery systems. Compatibility of the product with commercial delivery systems that were used in the clinical studies was demonstrated. Following questions from the

Delegate,[12] the sponsor has identified products registered in Australia that states are suitable for use with pegcetacoplan.

Sterility and endotoxin aspects were found to be acceptable.

The drug product is contained in 20 mL vials each vial containing 1080 mg of pegcetacoplan as the active substance, dissolved in water for injections (54 mg pegcetacoplan per mL).

The product is administered undiluted, and instructions for use are included in the PI.

The finished product specifications are sufficient to ensure the quality of the finished product at release and throughout the shelf life. A shelf-life of 12 months when stored at 2 to 8°C, with the conditions 'Refrigerate. Do not freeze. Protect from light' is supported by the product stability data.

The composition of the formulation used in Phase II and Phase III clinical studies is the same as the commercial presentation.

Any outstanding quality issues have been resolved prior to approval. Chemistry and quality control aspects are considered acceptable.

The quality evaluation had no objections to the approval of pegcetacoplan from a quality perspective.

Nonclinical

The nonclinical evaluator raised no objections to the registration of pegcetacoplan. The submitted nonclinical data were appropriate, given the species specificity of its pharmacology (primates) and its PEGylated structure (PEG40 (polyethylene glycol (PEG) 40 kDa molecular weight) backbone). The overall quality of the nonclinical dossier was high. As pegcetacoplan is primate-specific in its action several studies were omitted from the submission. This was acceptable to the evaluator. A summary of the findings of the nonclinical evaluation is included in this section.

Pegcetacoplan is the first in a pharmacological class of compstatin based complement C3 protein inhibitors. It consists of two 15 amino acid cyclic synthetic peptides conjugated to a linear PEG chain. The peptidic domains of the molecule are a derivative of compstatin, a 13 amino acid cyclic peptide that was shown to bind to human and primate C3 and C3b, resulting in broad inhibition of complement activation.

In vitro, pegcetacoplan bound complement components C3 and C3b, with affinities of 15.6 nM and 21.3 nM, respectively. Pegcetacoplan also inhibited the alternative and classical pathways of complement activation *in vitro*, with concentration required to achieve half (50%) maximal response (EC_{50}) values of 136 nM and 64 nM (in human serum) and 208 nM and 92 nM (in monkey serum), respectively. *In vivo*, pegcetacoplan decreased C3a levels and increased C3 levels (reflecting decreased C3 consumption) and inhibited functional complement measurements (classical complement pathway haemolytic activity assay (CH50);[13] and alternative complement pathway haemolytic activity assay (AH50)[14]) in cynomolgus monkeys, with greater effects on the latter (alternative) pathway.

[12] See Question 1 under Questions for the sponsor section of the AusPAR for further details.
[13] **Classical complement pathway haemolytic activity assay (CH50)** assesses the classical complement pathway including early components that activate the pathway in response to immune complexes (C1q, C2 and C4) and the terminal complement components (C3, C5, C6, C7, C8, C9) involved in the formation of the membrane attack complex
[14] **Alternative complement pathway haemolytic activity assay (AH50)** is a screening for complement activity in the alternative pathway that shares C3 and C5 to C9 with the classical pathway but has the early

No potential clinically relevant hazards were identified in the safety pharmacology studies. In conscious cynomolgus monkeys no significant inhibition of hERG potassium channel tail current was observed with pegcetacoplan or PEG40 at clinically relevant concentrations, indicating a lack of torsadogenic potential. No adverse effects on body temperature, hemodynamic, electrocardiographic, or respiratory parameters were seen at exposure levels similar to that anticipated clinically. Dedicated central nervous system safety pharmacology studies were not performed as pegcetacoplan did not distribute to the brain and no clinical signs indicative of altered neurobehavioral function were noted in the toxicology studies.

Overall, the pharmacokinetic (PK) profile in cynomolgus monkeys was qualitatively similar to that of humans. Pegcetacoplan was slowly absorbed with high bioavailability after subcutaneous dosing, with a time of maximum concentration (T_{max}) of 2 to 3 days and a long half-life ($t_{1/2}$) (7 to 9 days). The low volume of distribution of pegcetacoplan suggested restriction to the blood volume, and tissue penetration was negligible, with brain and spinal cord levels not detectable. Placental transfer and excretion into milk were demonstrated but were minimal (< 1%) and were not pharmacologically relevant.

No specific studies on the metabolism of pegcetacoplan have been conducted. Pegcetacoplan is expected to be subject to catabolism into small peptides and amino acids, similar to other PEGylated peptide or protein conjugates. While no human mass balance studies were performed, the predominant route of excretion in monkeys was urinary.

Pegcetacoplan has a low potential for PK drug interactions as it did not induce or inhibit cytochrome P450 (CYP450)[15] isozyme activities or serve as a substrate and/or inhibitor for human drug transporters.

Pegcetacoplan had a low order of acute toxicity in rabbits (subcutaneously) and monkeys (subcutaneously, intravenously). Repeat dose toxicity subcutaneous studies with pegcetacoplan and PEG40 in rabbits and monkeys of up to 6 to 9 months duration did not yield any findings of clinical concern. The main findings after 28 days, and 6 to 9 months of dosing consisted of non-reversible renal tubular degeneration and non-reversible multi-tissue histiocytic infiltration and macrophage vacuolation, accompanied by vacuolation of the choroid plexus epithelium. These effects occurred in animals at relative exposure levels (expressed as the monthly PEG40 load) of about 5 to 29 times that expected in humans at the maximum recommended human dose. As rabbits are a pharmacologically unresponsive species for this molecule and the findings occurred in the PEG40 alone groups, it is suggested the findings are attributable to the PEG40 moiety of pegcetacoplan.

There are no genotoxicity or carcinogenicity concerns for pegcetacoplan, as neither its peptide precursor nor PEG40 were mutagenic in the bacterial mutation assay or clastogenic *in vitro* (in human lymphocytes) or *in vivo* (in the mouse micronucleus test). Pegcetacoplan is not genotoxic, and there are no indications from the repeat dose toxicity studies of stimulation of cellular inflammatory or proliferative effects.

components of factors D, B and properdin and control factors H and I. This pathway can be activated by spontaneous hydrolysis or by microbial polysaccharides.

[15] **Cytochrome P450 (CYP)** enzymes: CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.

Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

The evaluator initially proposed a Pregnancy Category D;[16] but has agreed to Pregnancy Category B3;[17] after considering the counterproposal from the sponsor. The significant increase in abortions or stillbirths observed in the enhanced pre-postnatal study in cynomolgus monkeys occurred at exposure ratio based on area under the concentration-time curve (AUC) of 2.9, with a no observable effect levels (NOAEL) at an AUC-based exposure ratio of 1.3, and occurred in the absence of maternal toxicity. No maternal toxicity or teratogenic effects were observed in offspring delivered at term, and no developmental effects were observed in infants up to 6 months postpartum. Fertility and early embryonic development studies were not conducted with pegcetacoplan but there were no microscopic abnormalities in male or female reproductive organs in toxicity studies in rabbits and monkeys dosed daily subcutaneously for 28 days, or 6 months to 9 months at exposure levels up to approximately 4 to 6 times the clinical AUC. The sponsor has proposed Category B3 based on:

- there are no clinical data with pegcetacoplan in pregnant women;
- nonclinical findings are of unknown significance, as they occurred at systemic exposures approximately 3-fold human steady state;
- there is no obvious pharmacological liability with general complement inhibition and pregnancy, also shown in the clinical data and PI documents with other complement inhibitors such as Soliris and Ultomiris;
- the sponsor proposed Category B3 for pegcetacoplan due to the findings of increased stillbirths and abortions in pregnant cynomolgus monkeys at systemic exposures approximately 3-fold human steady state AUC;
- pegcetacoplan is not genotoxic, and in pilot studies in rats and rabbits (pharmacologically inactive but likely relevant to the PEG portion of the molecule), no teratogenicity or reproductive toxicity was noted;
- the NOAEL for reproductive toxicity was at exposures similar to (1.3 times) human steady state AUC; adverse findings were only noted at closer to 3-fold human exposures.

Pegcetacoplan was weakly immunogenic in rabbits and monkeys. As with other PEGylated medicines, hypersensitivity reactions or anaphylaxis are possible.

Clinical

The clinical dossier consisted of the following studies:

- Two Phase I studies: Study APL2-CP-PNH-204 (also known as the PADDOCK trial) and Study APL-CP0514 (also known as the PHAROAH trial)
- Three Phase II studies: Study APL2-202 (also known as the PALOMINO trial), Study APL2-CP-AIHA-208 and Study APL2-201
- Three Phase III Studies: Study APL2-307, Study APL2-308 and Study APL2-302 (also known as the PEGASUS trial)

[16] **Pregnancy Category D**: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
[17] **Pregnancy Category B3**: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Pharmacology

Pharmacokinetics

Data used to describe the PK of pegcetacoplan were derived from 9 studies: 4 in healthy subjects, one in subjects with renal impairment and 4 in patients with PNH, in addition to pharmacometrics studies. A summary of the findings follows:

- with single ascending doses of subcutaneous pegcetacoplan (45 to 1440 mg) in healthy subjects, absorption was slow (median T_{max} ranged from 4.5 to 6.0 days), exposure increased with dose proportional manner, geometric mean apparent clearance (CL/F) ranged from 11.1 to 17.2 mL/h, geometric mean apparent volume of distribution ranged from 3.6 to 4.8 L, and geometric mean terminal elimination $t_{1/2}$ ranged from 8.1 to 9.8 days. CL/F, volume of distribution and $t_{1/2}$ remained relatively constant over the dose range, suggesting single dose PK linearity over the dose range;
- bioavailability of the subcutaneous dose was approximately 87%;
- in a multiple ascending daily subcutaneous doses of pegcetacoplan from 30 to 270 mg for 28 days in healthy subjects, the geometric mean for AUC over a dosing interval and for C_{max} increased in a generally dose proportional manner. The geometric mean CL/F ranged from 15.7 to 20.7 mL/h, the geometric mean apparent volume of distribution ranged from 5.2 to 6.1 L, and the geometric mean terminal elimination $t_{1/2}$ ranged from 8.2 to 9.9 days. No time-dependent PK was evident;
- pegcetacoplan significantly accumulated after multiple dosing (1080 mg twice weekly), with the mean accumulation index of about 69 following 28 days of pegcetacoplan 270 mg/day administered subcutaneously;
- protein binding and erythrocyte distribution have not been specifically studied. The sponsor reported that, based on its nM binding affinity for C3, pegcetacoplan is expected to readily form 1:1 and 1:2 complexes with plasma C3, with the equilibrium strongly favouring the complexed forms as stoichiometry allows. The sponsor considered there is a low potential for distribution in RBCs and based on the small volume of distribution, distribution to the tissues is likely to be low;
- based on its PEGylated peptide structure the metabolism of pegcetacoplan is expected to occur via catabolic pathways with degradation into small peptides and amino acids;
- no impact of renal impairment on the PK of pegcetacoplan was demonstrated. No dedicated clinical studies investigated the effects of hepatic impairment, sex, or age on the PK of pegcetacoplan; no clinically meaningful differences were demonstrated between Japanese and non-Japanese patients;
- no clinical drug-drug interaction studies were undertaken, but *in vitro* absorption, distribution, metabolism, and excretion testing with CYP450 isozymes and transporter proteins suggested minimal potential for clinical drug-drug interactions;
- in the Week 48 update, 22 patients had continued from the Week 16 pegcetacoplan cohort. Serum concentrations were similar in the continuing pegcetacoplan patients (n = 22) and in the patients who switched from eculizumab (n = 18).

Population pharmacokinetics data

The PK of subcutaneous pegcetacoplan was adequately described by a one compartment disposition model with transit compartment absorption for subcutaneous administration, and first-order elimination in healthy adults, adults with renal impairment, and adults with PNH.

Based on population pharmacokinetic (PopPK) modelling inter-subject variability between healthy adults from predicted geometric coefficient of variation (CV) values (as a

percentage) after 1080 mg twice weekly subcutaneous administration were 23.4%, 23.7% and 23.7% for maximum concentration at steady state ($C_{max,ss}$), area under the concentration-time curve at steady state (encompassing the final dosing week), and average concentration during a dosing interval at steady state ($C_{avg,ss}$), respectively.

In adults with PNH, the model predicted median volume of distribution of the central compartment for of pegcetacoplan 1080 mg subcutaneously twice weekly was an estimated 3.84 L (90% prediction interval: 2.44, 6.42) and the predicted median clearance an estimated 0.0152 L/h (90% prediction interval: 0.0102, 0.0230). The central compartment volume of distribution was similar in patients with PNH and in healthy subjects, but clearance was greater in patients with PNH than in healthy subjects.

The median effective $t_{1/2}$ of pegcetacoplan subcutaneously at 1080 mg twice weekly was estimated to be 8.0 days in adult PNH patients compared to 10.1 days in healthy adults, reflecting the comparatively higher estimated systemic clearance in subjects with PNH.

Model simulations performed to assess the impact of covariates on predicted pegcetacoplan exposure identified baseline body weight was a significant covariate of both pegcetacoplan clearance and volume of distribution. Both clearance and volume of distribution increased non-linearly with increasing body weight, leading to lower predicted pegcetacoplan exposure at higher body weights. Other covariates of age, sex, Asian race, Japanese ethnicity, baseline creatinine clearance, baseline total bilirubin, baseline albumin, baseline aspartate aminotransferase, baseline alanine transaminase, eculizumab co-administration, and anti-drug antibodies were reported to have no statistically significant impact on pegcetacoplan exposure.

Pharmacodynamics

The key points from the evaluation of the pharmacodynamic studies and exposure response analyses are:

- complement C3 levels increased with increasing pegcetacoplan dose in both single and multiple dose subcutaneous studies in healthy subjects and subjects with PNH. An increase in serum C3 of more than 150% from baseline levels was observed at subcutaneous doses of 270 mg/day or higher, indicating that pegcetacoplan interacts with complement C3 and is likely to slow down its clearance from the circulation;
- in the pivotal Phase III study mean C3 concentrations in the pegcetacoplan group increased by around 280% at Week 2 relative to Baseline then stabilised to Week 16. C3 concentrations in the eculizumab group declined after the end of the run-in period and returned to baseline level at Week 8;
- repeated dosing of pegcetacoplan can achieve significant but not complete inhibition of the haemolytic activity via the alternative pathway. Mean AH50/AP50;[14] decreased from Baseline with increasing pegcetacoplan dose, and a decrease of ≥ 50% from Baseline was observed at subcutaneous doses of ≥ 270 mg/day;
- no meaningful effect on CH50;[13] was seen at any of the administered doses.
- Patients in the pegcetacoplan group recovered a significant level of complement haemolytic activity compared with the eculizumab group. Patient with prior treatment with eculizumab had CH50 and AH50 values that remained low and relatively unchanged if they continued eculizumab. Subjects who received pegcetacoplan monotherapy for 16 weeks had increased CH50 values that normalised to the range typically seen in healthy volunteers, and AH50 values that increased and stayed close to 50% of normal at Week 16;
- a decrease in Type I and Type II PNH red blood cells (RBCs) and an increase in Type III PNH RBCs during the 4-week run-in period and maintained during the 16-week was with pegcetacoplan group but not in the eculizumab. The increase in Type III PNH

RBCs indicate a reduction in haemolysis, and protection of the PNH RBCs corresponding to the rise in haemoglobin;

- the sum of mean clonal distribution of PNH RBCs (percent PNH Type II and Type III) was close to 95% of overall PNH RBCs in the pegcetacoplan group when approaching Week 16, suggesting repeated dosing of pegcetacoplan can preserve PNH Type II and Type III cells in PNH patients by preventing haemolysis;
- a reduction in C3 deposition, an indicator of RBC opsonisation and extravascular haemolysis, on Type II and III PNH RBCs was observed with pegcetacoplan but not eculizumab at Week 16, suggesting pegcetacoplan protects RBCs from complement mediated attack and extravascular haemolysis;
- no clinically meaningful effects on heart rate, PR duration, QRS duration, cardiac repolarisation (corrected QT interval (QTc),[18] or other electrocardiographic parameters were noted;
- in the Week 48 update, the patterns of change from Baseline seen in the pegcetacoplan group in the Week 16 analysis were seen in the patients that switched from eculizumab to pegcetacoplan including:
  - the percentages of Type I PNH, Type II PNH, and Type III PNH RBCs;
  - the sum of mean clonal distribution of PNH RBCs (percentage PNH Type II and Type III) approximated 90% of overall PNH;
  - the percentages of C3 deposition on Type I PNH, Type II PNH, and Type III PNH RBCs; and
  - the complement markers C3, mean AH50 and CH50.

Exposure-response modelling of pegcetacoplan and haemoglobin

The relationship between pegcetacoplan exposure and increase in haemoglobin level was adequately described using a sigmoidal maximal effect (E_{max}) direct effect model. E_{max} for haemoglobin level was a 36.3% increase from Baseline (8.6 g/dL) with an EC_{50} of 272 µg/mL.

The model supported the Phase III dose regimen of 1080 mg twice weekly as an effective dose for haemoglobin response. At this dose, around 40% of patients are predicted to achieve haemoglobin levels > 12 g/dL and at least 99% of the maximal predicted haemoglobin increase from Baseline.

Observed baseline haemoglobin level was found to be statically significant covariate of E_{max}. Individuals with lower baseline haemoglobin values are predicted to have a greater proportional increase in haemoglobin from Baseline.

Baseline creatinine clearance was a statically significant covariate of E_{max}. Individuals with renal impairment at Baseline (lower creatinine clearance) are predicted to have a smaller proportional increase in haemoglobin from Baseline. Predicted steady state median haemoglobin levels were 11.5 g/dL, 11.1 g/dL, 10.5 g/dL and 11.0 g/dL for subjects with baseline creatinine clearance values of ≥ 90 mL/min, 60-89 mL/min, 30 to 59 ml/min, and 15 to 29 mL/min, respectively. The sponsor considers that an increase in pegcetacoplan dose in patients with renal impairment is not warranted, as the median average pegcetacoplan concentration achieved with 1080 mg subcutaneously twice weekly is

[18] The **QT interval** is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.
The **corrected QT interval (QTc)** estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias.

approximately 99% of the maximal achievable haemoglobin response per level of renal function.

Sex, Asian race (including Japanese ethnicity), age, body weight, baseline eculizumab treatment status, and baseline C3 level are not anticipated to have clinically meaningful effects on the haemoglobin response to pegcetacoplan

Simulations of over or under delivery by 10% to 15% of the intended pegcetacoplan dose (1080 mg subcutaneously twice weekly) demonstrated that subcutaneous infusion dose delivery within this margin of error will not significantly impact the steady state haemoglobin level relative to precise delivery of the intended dose.

Exposure-response modelling of pegcetacoplan and lactate dehydrogenase levels

The relationship between pegcetacoplan exposure and decrease in lactate dehydrogenase (LDH) level was adequately described using a sigmoidal E_{max} direct effect model. The maximal effect was a 90.8% decrease from a baseline of 2117 IU/L with an EC_{50} of 173 µg/mL for patients without eculizumab treatment at Baseline. For subjects on eculizumab treatment at Baseline, the maximal effect was a 32.5% decrease from a baseline of 248 IU/L with an EC_{50} of 250 µg/mL.

The model supported the Phase III dose regimen of 1080 mg twice weekly being an effective dose for LDH response. Steady state pegcetacoplan serum concentrations are expected to achieve ≥ 95% and 99% of the maximal predicted LDH response for patients with and without eculizumab treatment at Baseline, respectively, with 71.6% of patients predicted to achieve LDH levels below the upper limit of normal.

Baseline eculizumab treatment status had an effect on baseline LDH, E_{max}, and EC_{50}. Median LDH levels at steady-state following pegcetacoplan 1080 mg twice weekly are predicted to be 231 IU/L for eculizumab naïve subjects and 177 IU/L for subjects with eculizumab treatment at Baseline corresponding to 78.4% and 97.4% of eculizumab-naïve and treated subjects achieving LDH control below 1.5 times the upper limit of normal, respectively.

Sex, Asian race (including Japanese ethnicity), age, body weight, baseline creatinine clearance, and baseline C3 level are not anticipated to have meaningful effects on the LDH response to pegcetacoplan

Simulations of over or under delivery by 10% to 15% of the intended dose demonstrated that subcutaneous infusion dose delivery within this margin of error will not significantly impact the steady-state LDH level relative to precise delivery of the intended dose.

Immunogenicity

Across all clinical studies, anti-pegcetacoplan peptide antibodies have been detected infrequently in pegcetacoplan treated subjects, and when detected these antibodies were generally transient. In the PEGASUS trial (Study APL2-302), anti-pegcetacoplan peptide antibody response was observed in 2 of 80 subjects (2.5%), including 39 subjects exposed to pegcetacoplan for 4 weeks during the run-in period only and 41 subjects exposed to pegcetacoplan up to Week 16.

Up to 82.5% of patients across the clinical studies had anti–PEG antibodies in the pre-dose sample. The incidence of treatment emergent or treatment boosted anti-PEG response were low, with many of those responses being transient. In the PEGASUS trial one subject developed a transient treatment-boosted anti-PEG antibody response (> 4-fold increase in titre from pre-dose level) and another developed a treatment emergent anti-PEG antibody response.

There are no apparent associations between antibody development and changes in the PK, efficacy, or safety profiles of pegcetacoplan.

In the Week 48 update, two (2.5%) patients had treatment emergent anti–pegcetacoplan peptide antibodies, both on a single measurement day but not at Baseline or other time points including in the open label period. At Week 16 both were neutralising antibody positive. However, no reductions in systemic pegcetacoplan exposure or clinical efficacy were observed in these subjects. Two (2.5%) patients developed treatment emergent anti-PEG antibodies. Four (5.0%) patients had treatment-boosted anti-PEG antibodies.

Dose in the pivotal study

The dose selected for the pivotal PEGASUS trial (Study APL2-302) was based on data from Studies APL2-202, APL2-CP-PNH-204, and APL-CP0514 from 30 patients with PNH. These studies demonstrated a dose dependent relationship of haematological responses of 270 mg/day to 360 mg/day. To reduce the burden of daily dosing and to promote compliance twice weekly dosing was investigated. The dosing regimen of 1080 mg/twice weekly or every three days were based on projected exposures for the 270 mg and 360 mg doses.

The formulation used in the PEGASUS trial is the one proposed for marketing.

Efficacy

Efficacy was supported by data from:

- Study APL2-302, a Phase III pivotal study, Week 16 data in initial submission, Week 48 update in response to TGA questions for the sponsor;
- Study APL2-CP-PNH-204, a Phase Ib ascending dose study;
- Study APL2-202, a Phase IIa open label study in eculizumab naïve patients;
- Study APL-CP0514, a Phase Ib single and multiple dose ascending study in patients who were anaemic despite eculizumab treatment.

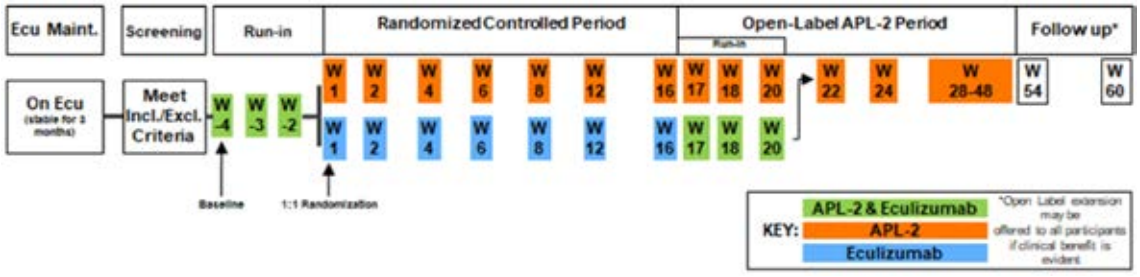
Study APL2-302

Study APL2-302 (the PEGASUS trial) was a prospective, randomised, multicentre, open label, active comparator, controlled Phase III study, that compared pegcetacoplan 1080 mg twice weekly and eculizumab in 80 adult patients with PNH with haemoglobin levels haemoglobin levels < 10.5 g/dL despite stable treatment with at least 3 months of eculizumab.

Study design

The first patient's first visit was on 14 June 2018 and the last patient completed the Week 16 analysis on 14 November 2019. The data cut-off date for this analysis was on 24 December 2019 for the Week 16 analysis; and 6 November 2020 for the Week 48 update. The clinical study report date was on 15 May 2020, with the Week 48 update on 1 April 2021. The study was conducted at 44 sites across 11 countries.

Figure 1: Study APL2-302 (PEGASUS trial) Study design



Abbreviations: APL-2 = sponsor's company development code for pegcetacoplan; Ecu = eculizumab, Excl. = exclusion; Incl. = inclusion; W = Week.

Details of the study design are listed below:

- 102 subjects screened, 80 randomised.
- All patients on a stable dose of eculizumab for at least 3 months prior to screening.
- 4-week run-in period of pegcetacoplan for all patients to reduce risk of haemolysis after withdrawal of eculizumab.
- Treatment arms:
  - pegcetacoplan (investigative treatment arm): 41 subjects were randomised to receive pegcetacoplan 1080 mg subcutaneously twice weekly as monotherapy; 2 of 41 subjects had dose increased to 1080 mg subcutaneously three times weekly because of LDH ≥ 2 x upper limit of normal (ULN).
  - eculizumab (active comparator arm: 39 subjects were randomised to receive eculizumab as monotherapy at their current stable dose.
- Mean treatment compliance to Week 16 was 100% in the eculizumab group and 99.4% in the pegcetacoplan group.
- Patient flow as at Week 16:
  - all patients received at least one dose of allocated treatment
  - discontinued treatment: 3/41 (7.3%) pegcetacoplan; 0% eculizumab arm
  - discontinued treatment due to adverse events: 3/41 (7.3%) pegcetacoplan; 0% eculizumab arm
  - withdrawn from study: 1/41 pegcetacoplan (2.4%); 0% eculizumab arm
  - completed Week 16 of study: 38/41 (92.7%) pegcetacoplan; 39/39 (100%) eculizum arm
  - at the end of the Week 16 randomised controlled period patients could enter the open label period where all received pegcetacoplan.

At the end of Week 48 patients could enter extension Study APL2-307. Patient not entering Study APL2-307 were followed for an additional 12 weeks (total 72 weeks in the study).

Key inclusion criteria

- Primary diagnosis of PNH confirmed by high sensitivity flow cytometry
- On treatment with eculizumab. Dosage of eculizumab stable for ≥ 3 months
- Haemoglobin < 10.5 g/dL at screening visit
- Absolute reticulocyte count (ARC) > 1 x ULN
- Platelet count > 50 x 10^6/mL
- Absolute Neutrophil Count > 500/mm^3
- Vaccination against *Neisseria meningitidis* type A, C, W, Y and Z; *Streptococcus pneumoniae*; *Haemophilus influenzae* type B ≤ 2 years from Day 1 dosing or within 14 days of pegcetacoplan treatment (unless acceptable antibody titres)
- Age ≥ 18 years, body mass index < 35 kg/m^2, written consent, can self-administer drug

Key exclusion criteria

- Active bacterial infection not resolved within a week of the first pegcetacoplan dose

- Receiving iron, folic acid, vitamin B12 and erythropoietin unless dosage stable 4 weeks before screening
- Hereditary complement deficiency
- Bone marrow transplantation
- Hypersensitivity to compound in product
- Potential confounders for cardiovascular outcome such as:
  - Arrhythmias or antiarrhythmic use
  - Certain conduction defects
  - Use of medication known to affect corrected cardiac QT interval (QT_c)
  - Coronary arterial disease, myocardial infarction, congestive heart failure requiring hospitalisation and/or intervention within 3 months
  - New York Heart Association heart failure classification ≥ Class 2
  - ≥ Class 2 angina pectoris
  - Cerebrovascular disease

Endpoints

Primary endpoint

Change from Baseline to Week 16 in haemoglobin level, excluding data before randomisation, and censored for transfusion (analysis by mixed model repeated measures with missing at random, intention-to-treat (ITT)[19] population).

Key secondary

These were assessments of non-inferiority to eculizumab based on pre-specified non-inferiority margins, using the ITT population. Superiority assessment to follow all non-inferiority assessments.

- Transfusion avoidance (yes/no outcome), defined as the proportion of subjects who did not require a transfusion during the randomised controlled period.
- change from Baseline to Week 16 in absolute reticulocyte count (ARC), excluding data before the randomised controlled period.
- change from Baseline to Week 16 in lactate dehydrogenase (LDH) level, excluding data before the randomised controlled period.
- change from Baseline to Week 16 in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale;[20] (Version 4) score, excluding data before the randomised controlled period.

[19] The randomised clinical trials analysed by the **intention-to-treat (ITT)** approach provide unbiased comparisons among the treatment groups. In the ITT population, none of the subjects are excluded, regardless of treatment compliance or attrition due to dropout or crossover, and the subjects are analysed according to the randomisation scheme. A **modified intention-to-treat analysis (mITT)** may sometimes be conducted excluding subjects post-randomisation.

[20] The **Functional Assessment of Chronic Illness Therapy (FACIT)** - Fatigue Scale is a 40-item measure that assesses self reported fatigue and its impact upon daily activities and function. It was developed for more precise evaluation of fatigue associated with anaemia in cancer patients.

Statistical analysis

Study population was randomised in a 1:1 ratio to pegcetacoplan or active comparator; randomised was stratified by number of packed RBC transfusions within 12 months before run-in (< 4, ≥ 4 transfusions); and platelet count (< 100,000/mm^3, ≥ 100,000 mm^3).

Enrolment was planned for 70 patients. A sample size of 64 (32 in each group) provides 90% power (using a 2-sided test at the 5% level of significance) of obtaining a statistically significant difference between the groups with the primary endpoint of Week 16 change from Baseline in haemoglobin level, assuming between pegcetacoplan and eculizumab of 1 g/dL and a standard deviation for the change from Baseline of 1.2 g/dL (effect size = 0.833 (that is, treatment difference of 1 g/dL divided by the standard deviation of 1.2 g/dL)). The additional patients were to account for a loss of power due to discontinuations.

The first assessments of the key secondary endpoints were for non-inferiority to eculizumab based on pre-specified non-inferiority margins, using the ITT population. Superiority assessment to follow all non-inferiority assessments.

Adjustments for multiple comparisons were made for the primary and key secondary endpoints. No adjustment was made for the other secondary endpoints and the results are considered exploratory from a statistical perspective.

Protocol amendments and deviations

Protocol deviations occurred in 73.8% of patients. Most (48.8% of the pegcetacoplan group and 64.1% of the eculizumab group) were due to study assessment /schedule non-compliance and were considered minor. Four patients from the pegcetacoplan group and two patients from the eculizumab group were excluded from the per protocol analysis set due to violations of the inclusion and exclusion criteria.

The baseline characteristics of the two randomised groups are summarised in Table 3 below.

Table 3: Study APL2-302 (PEGASUS trial) Summary of Baseline characteristics of patients in randomised controlled period

Baseline demographics and disease characteristics		Pegcetacoplan (n = 41)	Eculizumab (n = 39)
Age	Mean, years (SD)	50.2 (16.29)	47.3 (15.81)
Age group	< 65 years ≥ 65 years	31 (75.6%) 10(24.4%)	32 (82.1%) 7 (17.9%)
Sex	Male	14 (34.1%)	17 (43.6%)
	Female	27(65.9%)	22 (56.4%)
Race	White Asian Not reported	24 (58.5%) 5(12.2%) 10 (24.4%)	25 (64.1%) 17 (17.9%) 6(15.4%)
Weight	Mean, kg (SD)	75.86 (18.765)	74.6 (16.615)
Time since PNH diagnosis	Mean, years (SD)	8.74 (7.364)	11.68 (9.582)

Baseline demographics and disease characteristics		Pegcetacoplan (n = 41)	Eculizumab (n = 39)
Duration of eculizumab treatment to first dose pegcetacoplan	Median, days (SD)	1863.3 (1568.19)	1745.9 (1326.74)
Baseline eculizumab dose and regimen	900mg IV Q2W 900mg IV every 11 days 1200 mg IV Q2W 1500 mg IV Q2W	26 (63.4%) 1 (2.4%) 12(29.3%) 2 (4.9%)	30 (76.9%) 0 9 (23.1%) 0
Transfusions in prior 12 months	< 4 ≥ 4	20 (48.8%) 21 (51.2%)	16 (41.0%) 23 (59.0%)
Baseline lab results	Haemoglobin (g/dL), mean (SD)	8.69 (1.075)	8.68 (0.886)
	Absolute reticulocyte count (10^9 cells/mL), mean (SD)	217.52 (74.964)	216.15 (69.136)
	Lactate dehydrogenase (U/L), mean (SD)	257.48 (97.648)	308.64 (284.842)
	Haptoglobin (g/L), mean (SD)	0.144 (0.125)	0.125 (0.116)
	Total bilirubin (µmol/L), mean (SD)	42.52 (31.47)	40.51 (26.639)
	Indirect bilirubin (µmol/L), mean (SD)	34.65 (28.49)	32.89 (22.97)
	Number of patients with total platelet count < 100,000 mm^3, (% of treatment arm)	12 (29.3%)	9 (23.1%)
Medial history at screening	Iron overload Aplastic anaemia Haemoglobinuria Haemolysis	9 (22.0%) 11(26.8%) 5 (12.2%) 3 (7.3%)	12 (30.8%) 9 (23.1%) 3 (7.7%) 5 (12.8%)

Abbreviations: IV = intravenous; n = sample size; PNH = paroxysmal nocturnal haemoglobinuria; Q2W = once every 2 weeks; SD = standard deviation.

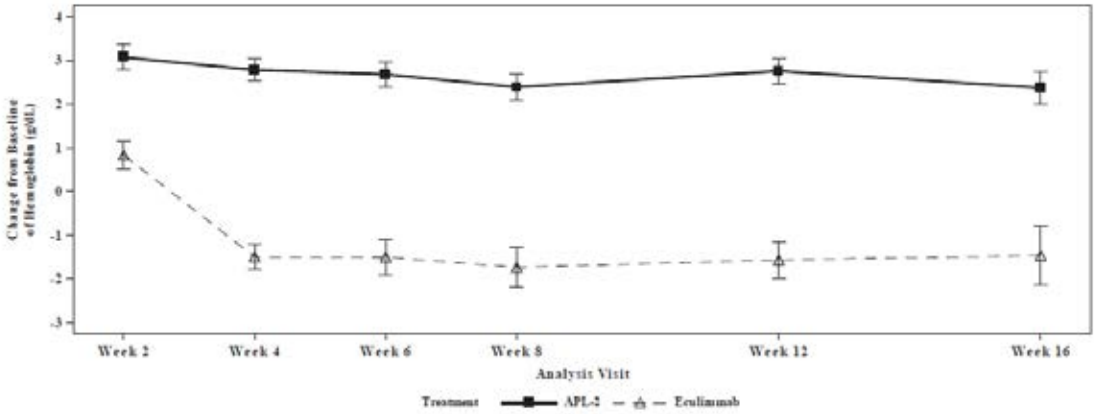
Randomised period Week 16 results

Primary endpoint

Change from Baseline in haemoglobin at Week 16 in the ITT population, censored for transfusion: Adjusted least square mean (LSM) change from Baseline in the haemoglobin

= 2.37 g/dL in the pegcetacoplan group and -1.47 g/dL in eculizumab (LSM difference 3.84 g/dL (95% confidence interval (CI): 2.33, 5.34); p < 0.0001).

Figure 2: Study APL2-302 (PEGASUS trial) Least square mean (standard error) change from Baseline in haemoglobin during randomised period, censored for transfusion (intention-to-treat set)



Abbreviation: APL-2 = sponsor's company development code for pegcetacoplan.

Sensitivity analyses for imputation method and supportive analyses using the ITT set, all available data, a modified intention-to-treat (mITT)[19] population, per protocol and the Week 16 completers sets all found similar results. Subgroup analyses were conducted, and while in general numerically favouring pegcetacoplan, the small numbers preclude firm conclusions.

Key secondary outcomes

The outcomes were tested first for non-inferiority then superiority.

Transfusion avoidance (yes/no):

- Pegcetacoplan (85.4% (35/41)) versus eculizumab group (15.4% (6/39)), absolute risk difference 62.53% (95% CI: 48.30%, 76.77%). Pegcetacoplan non-inferior to eculizumab based on non-inferiority margin -20%.

Absolute reticulocyte count (ARC) for change from Baseline to Week 16:

- Adjusted mean (standard error) change from Baseline to Week 16 in ARC was -135.82 (6.543) x 10^9 cells/L for pegcetacoplan versus 27.79 (11.859) x 10^9 cells/L for eculizumab. LSM difference was -163.61 x 10^9 cells/L (95% CI (-189.91, -137.30); nominal p-value < 0.0001). Upper bound of 95% CI less than pre-specified non-inferiority margin of 10 x 10^9 cells/L.

Lactate dehydrogenase change from Baseline to Week 16:

- Adjusted mean change from Baseline was -14.76 U/L for pegcetacoplan versus -10.12 U/L for eculizumab. LSM difference was -4.63 (95% CI (-181.30, 172.04); nominal p-value = 0.9557). Upper bound of the 95% CI of the adjusted treatment difference was not less than the pre-specified non-inferiority margin of 20. Not non-inferior so testing in the statistical hierarchy did not proceed.

Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Score:[20]

- Adjusted mean change from Baseline to Week 16 of the FACIT-Fatigue Score was 9.22 points for pegcetacoplan versus -2.65 points for eculizumab. LSM difference between treatment groups was 11.87 points (95% CI (5.49, 18.25); nominal p-value = 0.0005). This would have met the pre-specified non-inferiority margin of -3.

Week 48 results

Change from Baseline and change from Week 17 to Week 48 for haemoglobin level, absolute reticulocyte count (ARC), LDH level, packed RBC transfusion (Weeks 10 to 48; and Weeks 20 to 48) and patient related outcomes were secondary outcomes for the study. Patients could continue pegcetacoplan in Study APL2-307 at Week 48, but due to coronavirus disease 2019 (COVID-19) restrictions some patients who had elected to continue in the study were unable, therefore some patients were allowed to continue the open label period of the PEGASUS trial prior to entering Study APL2-307. Data from two patients who obtained pegcetacoplan compassionately were included in the follow-up period.

During the open label period three patients from the initial pegcetacoplan patient group and seven from the original eculizumab group withdrew from study treatment (mostly due to adverse events (AEs)).

At Week 48, the mean (standard deviation (SD) observed haemoglobin levels were as follows:

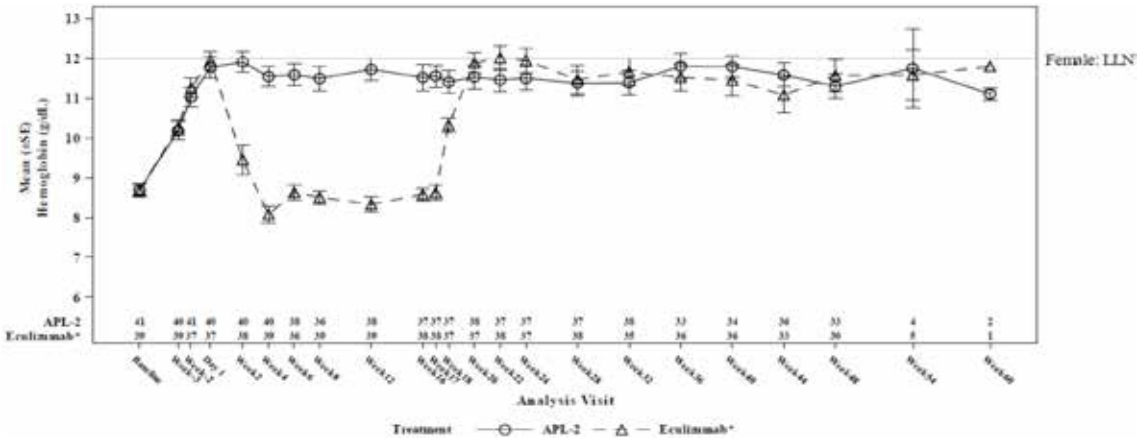
- Pegcetacoplan group (n = 33): 11.30 (1.77) g/dL
- Eculizumab/pegcetacoplan group (n = 30): 11.57 (2.21) g/dL
- Total open label period pegcetacoplan group (n = 63): 11.43 (1.98) g/dL

At Week 48, the mean (SD) changes from baseline haemoglobin level were as follows:

- Pegcetacoplan group (n = 33): 2.47 (1.72) g/dL
- Eculizumab/pegcetacoplan group (n = 30): 2.93 (2.09) g/dL
- Total open label period pegcetacoplan group (n = 63): 2.69 (1.91) g/dL

A similar change in haemoglobin was seen regardless of the baseline packed RBC transfusion stratum. A greater improvement in haemoglobin (approximately 1 g/dL across both groups) was seen in patients with lower baseline platelets, in both randomised groups, by Week 48.

Figure 3: Study APL2-302 (PEGASUS trial) Mean (± standard error) haemoglobin level by study periods and treatment groups (intention-to-treat set)



Abbreviations: APL-2 = sponsor's company development code for pegcetacoplan; LLN = lower limit of normal; SE = standard error.

Both treatment groups are in run-in period from Week -3 to Day 1. Only eculizumab subjects were on run-in period from Week 17 to Week 20.

* Eculizumab: subjects who were randomised to the eculizumab group in the randomised controlled period received pegcetacoplan in addition to eculizumab for 4 weeks (week 17 to 20) during the open

label period, and then received pegcetacoplan monotherapy. For central laboratory, haemoglobin (g/dL) limit ranges (12, 16) for female, and (13.6, 18) for male.

Week 48 observed absolute reticulocyte count (ARC) (mean (SD)):

- pegcetacoplan group (n = 31): 79.95 (26.77) × 10^9/L
- eculizumab/pegcetacoplan group (n = 29): 94.02 (50.06) × 10^9/L
- total open label period pegcetacoplan group (n = 60): 86.75 (40.05) × 10^9/L

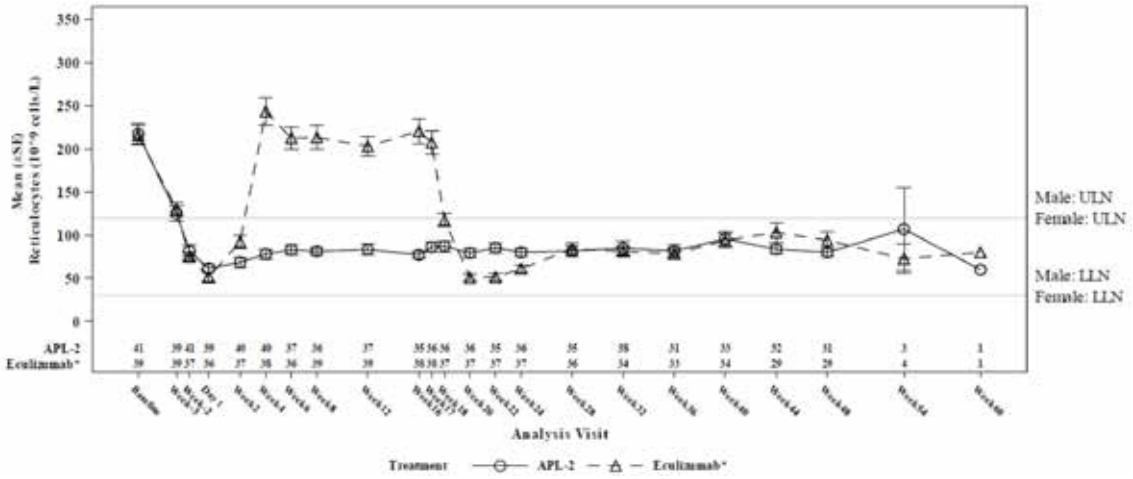
Week 48 changes from baseline ARC (mean (SD)):

- pegcetacoplan group (n = 31): -135.64 (67.90) × 10^9/L
- eculizumab/pegcetacoplan group (n = 29): -128.22 (59.60) × 10^9/L
- total open label period pegcetacoplan group (n = 60): -132.05 (63.59) × 10^9/L

Week 48 ARC normalisation:

- pegcetacoplan group (n = 41): ARC normalisation in 26 patients (63.4%)
- eculizumab/pegcetacoplan group (n = 39): ARC normalisation in 23 subjects (59.0%)

Figure 4: Study APL2-302 (PEGASUS trial) Observed mean (± standard error) absolute reticulocyte count by study period and treatment groups (intention-to-treat population)



Abbreviations: APL-2 = sponsor's company development code for pegcetacoplan; LLN = lower limit of normal; SE = standard error; ULN = upper limit of normal.

Both treatment groups are in run-in period from Week -3 to Day 1. Only eculizumab subjects were on run-in period from Week 17 to Week 20.

* Eculizumab: subjects who were randomised to the eculizumab group in the randomised controlled period received pegcetacoplan in addition to eculizumab for 4 weeks (Week 17 to 20) during the open label period, and then received pegcetacoplan monotherapy.

Reticulocytes limit ranges (male and female): 30 to 120 x 10^9 cells/L.

Week 48 observed lactate dehydrogenase (LDH) levels (mean (SD)):

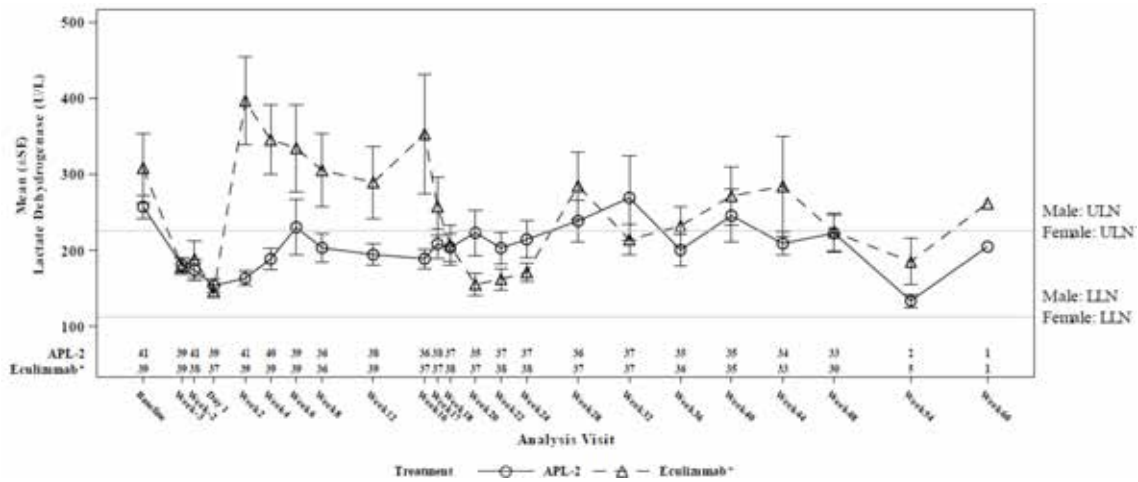
- pegcetacoplan group (n = 33): 222.67 (141.10) U/L
- eculizumab/pegcetacoplan group (n = 30): 224.08 (133.52) U/L
- total open label period pegcetacoplan group (n = 63): 223.34 (136.43) U/L

Week 48 changes from Baseline in LDH level (mean (SD)):

- pegcetacoplan group (n = 33): -41.53 (153.68) U/L

- eculizumab/pegcetacoplan group (n = 30): -105.27 (315.59) U/L
- total open label period pegcetacoplan group (n = 63): -71.88 (244.55) U/L

Figure 5: Study APL2-302 (PEGASUS trial) Observed mean (± standard error) lactate dehydrogenase level by study period and treatment group (intention-to-treat set)



Abbreviations: APL-2 = sponsor's company development code for pegcetacoplan; LLN = lower limit of normal; SE = standard error; ULN = upper limit of normal.

Both treatment groups are in run-in period from Week -3 to Day 1. Only eculizumab subjects were on run-in period from Week 17 to Week 20.

* Eculizumab: subjects who were randomised to the eculizumab group in the randomised controlled period received pegcetacoplan in addition to eculizumab for 4 weeks (week 17 to 20) during the open label period, and then received pegcetacoplan monotherapy.

Lactate dehydrogenase (U/L) limit ranges: 113 to 226 (male and female).

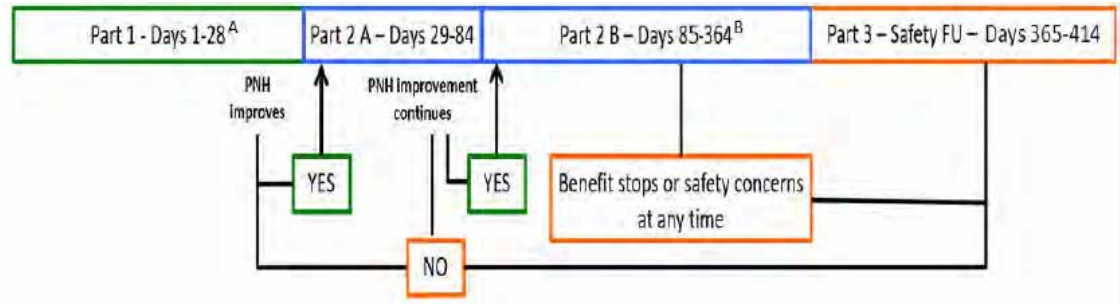
Similar patterns were seen in the FACIT-Fatigue Scale Score, perceived level of functioning from Linear Analog Scale Assessment (LASA) Scores,[21] and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Scale (QLQ-C30).[22]

Study APL2-CP-PNH-204

Study APL2-CP-PNH-204 (the PADDOCK trial) was a Phase Ib, open label, multi-centre, multinational, multiple ascending dose, study of subcutaneous pegcetacoplan in patients with PNH who had not previously been treated with eculizumab, that tested doses up to 360 mg/day. The study was conducted in two Cohorts and three parts.

[21] The **Linear Analog Scale assessment (LASA) Score** consists of five single items asking respondents to rate, on zero to ten scales, their perceived level of functioning.
[22] **European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Scale (QLQ-C30)** is a health related quality of life questionnaires in cancer research, which assesses important functioning domains (including physical, emotional and role) and common cancer symptoms (for example, fatigue, pain, nausea, vomiting and appetite loss).

Figure 6: Study APL2-CP-PNH-204 (PADDOCK trial) Study design



Abbreviations: FU = follow-up; PNH = paroxysmal nocturnal haemoglobinuria.

A. After completion of Part 1, Cohort 1 subjects proceeded immediately to Part 3; no Cohort 1 subjects progressed to Part 2A.

B. After completion of Part 2B, subjects could continue treatment with pegcetacoplan by transitioning to an open label extension study or Part 2C if enrolment into the extension study was not yet available. For these subjects, the Day 365 visit was also the first visit of the open label extension study or Part 2C. Subjects who elected to enrol in the open label extension study did not complete Part 3.

Cohort 1 comprised three patients; Cohort 2 comprised 20 patients. Cohort 2 patients dose at least 270 mg/day are considered the most relevant to the proposed indication and dosing.

The primary efficacy endpoints were change from Baseline in lactate dehydrogenase (LDH), haptoglobin and haemoglobin levels.

Table 4: Study APL2-CP-PNH-204 (PADDOCK trial) Primary efficacy endpoint results for Cohort 2

Parameter	Day	Number of subjects	Mean (SD)	Change from Baseline mean (SD)	Normalised levels
LDH (U/L)	Day 1 (Baseline)	20	2226.5 (1014.13)	−2105.2 (1078.79) 95% CI: −2659.8 to −1550.5	12 (70.6%) subjects with levels ≤ LLN
	Day 365	17	306.5 (324.67)		
Haptoglobin (g/L)	Day 1 (Baseline)	20	0.043 (0.0134)	0.066 (0.1245) 95% CI: 0.002 to 0.131	3 (17.6%) subjects with levels ≥ LLN
	Day 365	17	0.110 (0.123)		
Haemoglobin (g/dL)	Day 1 (Baseline)	20	8.38 (1.828)	3.68 (2.690) 95% CI: 2.29 to 5.06	8 (47.1%) subjects with levels ≥ LLN
	Day 365	17	12.14 (2.002)		

Abbreviations: CI = confidence interval; LDH = lactate dehydrogenase; LLN = lower limit of normal; SD = standard deviation.

The secondary efficacy endpoints were change from Baseline in FACIT-Fatigue Score;[20] change from Baseline in absolute reticulocyte count (ARC), and number of RBC transfusions per month. Results for Cohort 2, 270 mg/day were:

- Change from Baseline in mean FACIT-Fatigue score:
  - The mean change was 7.8 points at Day 29, 9.0 points at Day 85, and 7.1 points at Day 365.

    An increase in mean FACIT-Fatigue score of ≥ 3 points is generally accepted as being clinically meaningful.
- Change from Baseline in mean absolute reticulocyte count (ARC):
  - From a baseline mean ARC of 194.9 x 10^9 cells/L (> 1.5 x ULN), mean ARC decreased to within the normal range with 14 (70%) subjects exhibiting normal ARC.
  - There were fluctuations in mean ARC, but the mean remained below Baseline and was < 1.5 x ULN at Day 533 (mean of 121.5 x 10^9 cells/L).
- Transfusion avoidance:
  - In the 12 months prior to screening 18 of 20 patients received one or more transfusions with 11 of 20 patients receiving more than 4 transfusions. Most (13 of 20 patients) required no transfusion. Of the 7 of 20 patients who were transfused after starting pegcetacoplan, two were transfused prior to pegcetacoplan reaching steady-state concentration and five after pegcetacoplan had reached steady state concentration.

Study APL-CP0514

Study APL-CP0514 (the PHAROAH trial) was an open label, single and multiple dose study, safety, tolerability, and pharmacology study in 4 Cohorts. The final Cohort received pegcetacoplan at 270 mg/day for 729 days, increased to 360 mg/day if clinically indicated. FACIT-Fatigue Scale was the only (exploratory) efficacy endpoint specified in the study.

Study APL2-202

Study APL2-202 (the PALOMINO trial) was a Phase IIa, open label, multidose study of subcutaneous pegcetacoplan 270 mg subcutaneously daily in patients with PNH previously treated with eculizumab. Only four of a planned 20 patients were enrolled in this study.

Safety

The safety of pegcetacoplan is supported by data from the PNH program and limited additional data from other studies (Study APL2-307, Study APL2-308), and the open label phase of the pivotal Phase III controlled study, Study APL2-302 (the PEGASUS trial) are ongoing.

Cumulatively, 142 patients with pegcetacoplan who were exposed to at least one dose of pegcetacoplan. Of those 113 were exposed to more than 3 months treatment, 95 patients received over 6 months therapy, 36 patients received over one year of therapy, 9 patients received over 2 years of therapy, 4 patients received over 3 years of therapy.

The main available safety information arises from Study APL2-302 (the PEGASUS trial), with additional data from the Week 48 update from this trial.

The key safety information from the PEGASUS trial including the additional safety information from the Week 48 update is summarised in Table 5 below.

Table 5: Study APL2-302 (PEGASUS trial) Summary of safety findings

	Randomised period		Open label period	Total
	pegcetacoplan (n=44)	eculizumab (n=39)	pegcetacoplan (n=28)	Overall pegcetacoplan monotherapy
Exposure				
Median duration of exposure, days (SD)	107. 2 (18.61)	100.2 (4.21)	209.8 (39.18)	258.3 (91.16)
Total number of infusions	1279	316	4707	5986
Pegcetacoplan infusions interrupted	7	-	7	14
Deaths				
Fatal TEAE, n (%)	0	0	1	1
Treatment-emergent adverse events				
Subjects with at least one TEAE, %	36 (87.8%)	36 (92.3%)	71 (92.2%)	78 (97.5%)
Most common treatment-emergent adverse events (> 10% in either arm)				
Injection site erythema, %	17.1	0	11.7	16.3
Fatigue, %	4.9	15.4	10.4	12.5
Pyrexia, %	4.9	2 .6	7.8	10.0
Injection site pruritus, %	2.4	0	6.5	7.5
Asthenia, %	7.3	12.8	5.2	6.3
Injection site reaction, %	9.8	0	2.6	6.3
Injection site swelling, %	9.8	0	1.3	6.3
Nasopharyngitis, %	7.3	5.1	15.6	17.5
Upper respiratory tract infection, %	2.4	2.6	10.4	11.3
Diarrhoea, %	22.0	5.1	14.3	21.3
Abdominal pain, %	9.8	10.3	5.2	10.0
Vomiting, %	0	10.3	3.9	3.8
Haemolysis, %	12.2	25.6	19.5	23.8

	Randomised period		Open label period	Total
	pegcetacoplan (n=44)	eculizumab (n=39)	pegcetacoplan (n=28)	Overall pegcetacoplan monotherapy
Anaemia, %	0	15.4	2.6	2.5
Arthralgia, %	4.9	5.1	7.8	10.0
Back pain, %	7.3	10.3	2.6	6.3
Cough, %	2.4	2.6	11.7	12.5
Headache, %	4.9	23.1	10.4	13.8
Dizziness, %	2.4	12.8	3.9	3.8
Serious treatment-emergent adverse events (serious adverse events)				
Subjects with at least one serious adverse event, n (%)	7 (17.1%)	5 (12.8%)	18 (23.4%)	24 (30%)
Most common serious adverse events (> 5% of patients)				
Haemolysis, %	4.9	2.6	6.5	8.8
Anaemia, %	0	5.1	0	0
Treatment-related adverse events (%)				
Subjects with at least one TRAE	34.1	17.9	44.2	48.8
Most common treatment-related adverse events (≥ 15% in either arm)				
Injection site erythema, %	14.6	0	11.7	15.0
Injection site induration, %	7.3	0	6.5	6.3
Injection site pruritus, %	2.4	0	5.2	6.3
Injection site reaction,%	9.8	0	2.6	6.3
Injection site swelling, %	9.8	0	1.3	6.3
Haemolysis, %	4.9	7.7	1.3	3.8
Headache, %	0	2.6	5.2	5.0
Back pain,%	0	5.1	0	0
Adverse events of special interest				
Injection site reaction, %	36.6	2.6	26.0	36.3

	Randomised period		Open label period	Total
	pegcetacoplan (n=44)	eculizumab (n=39)	pegcetacoplan (n=28)	Overall pegcetacoplan monotherapy
Thrombosis,%	0	0	2.6	2.5
Infection, %	29.3	28.2	55.8	60
Sepsis, %	0	0	3.9	3.8
Hypersensitivity, %	12.2	5.1	18.2	22.5
Adverse events leading to discontinuation (%)	7.3	0	11.7	15.0

Abbreviations: n = sample size; SD = standard deviation; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event.

Over 90% of the injection site reactions in the pegcetacoplan groups were mild, and none was severe.

Severe treatment-emergent adverse events (TEAEs) were reported in 18 (23.4%) subjects of the total open label period pegcetacoplan group; most commonly (≥ 2 patients) haemolysis (8 patients), acute kidney injury (3 patients), and haemolytic anaemia and acute respiratory failure (2 patients each). Severe TEAEs were reported in 8 patients in the randomised pegcetacoplan group: most commonly haemolysis (2 patients).

Infections were common in the treatment groups. Most were nasopharyngitis or upper respiratory tract infections. Urinary tract infection occurred in 7 patients in the overall pegcetacoplan group, and oral herpes in 6 patients. Gastroenteritis in 2 patients, upper respiratory tract infection, COVID-19 infection and diverticulitis in one patient each were considered serious adverse events (SAEs). Overall, 3 patients had sepsis, one each with post-procedural sepsis and biliary sepsis. The one death in the PEGASUS trial was due to COVID-19.

Thrombosis was reported in 2 patients, one with a deep vein thrombosis and one with a jugular vein thrombus. Neither were considered related to the study treatment.

Around 27% of patients in Cohort 2 had a clinically significant decline in renal function however the majority of these cases could be attributed to haemolysis.

Four patients had SAEs considered possible related to pegcetacoplan, and three SAEs considered possible related to pegcetacoplan (intestinal ischaemia, hypersensitivity pneumonitis and haemolytic anaemia all resolved). Hypersensitivity SAEs occurred in 2 patients (one event each of allergy to immunoglobulin therapy and hypersensitivity pneumonia).

Four of the patients with TEAEs that resulted in discontinuation had events considered related to pegcetacoplan (haemolysis, haemolytic anaemia, intestinal ischaemia, and hypersensitivity pneumonitis).

Similar safety findings were identified in the early phase clinical studies.

No formal studies have been conducted to investigate the pattern or time course of the return of the clinical consequences of PNH if pegcetacoplan is withdrawn. The sponsor recommends an alternative therapy should be considered and patients should be carefully observed for signs and symptoms of serious intravascular haemolysis.

Risk management plan

The sponsor has submitted draft EU-risk management plan (RMP) version 0.1 (7 August 2020; data lock point (DLP) 31 May 2020) and Australia specific annex (ASA) version 0.1 (October 2020) in support of this application. In its response to a TGA request for information, the sponsor has supplied updated draft EU-RMP version 0.1 (29 March 2021; DLP 31 May 2020) and ASA version 0.2 (11 June 2021). On request, sponsor has provided draft EU-RMP version 0.2 (23 July 2021; DLP 31 May 2020) and ASA version 0.3 (26 August 2021) to support the decision on product registration.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 6.[23]

Table 6: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks		–	–	–	–
Important potential risks	Serious infections	ü	ü[1,2]	ü	ü[3,4,5,6,7]
	Serious hypersensitivity reactions	ü	ü[1,2]	ü	ü[5,6]
	Intravascular haemolysis after drug discontinuation	ü	ü[1,2]	ü	ü[5,6]
	Immunogenicity	ü	ü[1,2]	ü	–
	Malignancies and haematologic abnormalities	ü	ü[1,2]	–	–
	Potential long-term effects of PEG accumulation	ü	ü[1,2]	–	–
Missing information	Use in patients with bone marrow failure	–	ü[2]	–	–
	Use in pregnant women	ü	ü[2]	ü	–
	Long-term safety (> 1 year)	ü	ü[1,2]	ü	–

1 Ongoing open label extension study (Study APL2-307)

2 Planned post-authorisation safety study (PASS) from International paroxysmal nocturnal haemoglobinuria (PNH) Interest Group (IPIG) PNH Registry information

[23] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

3 Boxed warning in Product Information (PI) and Consumer Medicines Information (CMI)

4 Patient Card

5 Guide for healthcare professionals

6 Patient/carer guide

7 Controlled access program and annual reminder of mandatory revaccinations in line with national guidelines

- Important potential risks and missing information as listed in the draft EU-RMP are the same as for Australia. There are no Australia specific safety concerns. At the second round of evaulation, a number of safety concerns are renamed in EU-RMP/ASA to provide better risk definition. 'Use in children' was removed as a missing information as this is not supported under proposed indication. 'Long-term safety (> 1 year)' has been added as missing information. At the third round of evaluation, 'Immunogenicity', 'Malignancies and haematologic abnormalities' and 'Potential long-term effects of PEG accumulation' have been added to the EU-RMP and ASA as important potential risks. The summary of safety concerns is considered acceptable.
- Routine and additional pharmacovigilance activities are proposed for all concerns. There is an ongoing open label extension study to establish long-term safety and efficacy for subjects completing a previous PNH pegcetacoplan study, addressing all important potential risks. There is a planned post-authorisation safety study (PASS) registry study to further characterise all RMP concerns and help inform efficacy of risk minimisation activities. Both activities have multinational recruitment, involve, and have safety applicability to Australian patients. Information collection will be from existing International Paroxysmal nocturnal haemoglobinuria Interest Group (IPIG) PNH Registry and is to include pregnancy complications, birth outcomes, breastfeeding, and infant outcomes in women exposed to pegcetacoplan during pregnancy. The sponsor proposes recruiting 300 patients over approximately 2 years, data collection commencing from January 2022, with a minimum of 3 years of follow-up. The sponsor has agreed to provision of the final study protocol (European Medicines Agency (EMA) agreed) as a RMP post-approval commitment.
- Routine risk minimisation activities are proposed for all concerns, with the exception of missing information on patients starting treatment with bone marrow failure which will be addressed in additional pharmacovigilance. The PI, Consumer Medicines Information (CMI) and Instructions for Use sheets will be included in the pack as a package insert. At the second round of evaluation, sponsor agreed to strengthen PI communication on use in pregnancy with proposed amendments.
- For the important potential risk of serious infections, sponsor agrees to the following additional risk minimisation activities as regulatory requirements to promote and support Empaveli's safe use in Australia:
  - System for controlled distribution in place to align with the ongoing risk preventative measure for other C5 inhibitors in Australia. The following requirement needs to be fulfilled before the product is dispensed: Submission of written confirmation of the patient's vaccination against *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenza* and/or prophylactic antibiotic treatment according to national vaccination guidelines.
  - An annual reminder of mandatory revaccinations sent to prescribers and dispensing pharmacists in accordance with current national vaccination guidelines.
  - Boxed warnings in PI and CMI.

  - An educational programme to address training, education, and supportive measures on the safe use of pegcetacoplan within and outside of the clinical setting. Proposed supporting educational materials include a health care professionals guide, a wallet-sized Patient Card, and a patient/carer guide to address concerns indicated in Table 6 above.

- Except for the boxed warnings (USA and Australia only), Australian and EU activities will be aligned. The sponsor is provided with flexibility to further develop and improve the implementation plan for the controlled distribution system and educational programme prior to product launch. The TGA must agree about the content and format of the controlled access and educational programmes prior to implementation, including communication media, distribution modalities, and any other aspects of the programmes.

Risk-benefit analysis

Delegate's considerations

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare condition and the numbers of patients in the clinical development plan reflects this. There are two complement-targeted options registered in Australia, but both are C5 inhibitors. Control of intravascular haemolysis is potentially achieved using C5 inhibitors, whereas the aim of C3 inhibition is to address intravascular and extravascular haemolysis. This submission seeks the registration of pegcetacoplan, a C3 inhibitor.

The primary evidence to support the efficacy of pegcetacoplan is Study APL2-302, also known as the PEGASUS trial, that compared eculizumab and pegcetacoplan in patients who were stable on eculizumab. Eculizumab is registered in Australia for use in PNH;[8] and is considered a reasonable comparator. All patients switched from eculizumab to pegcetacoplan for the run-in period and two further switches to and then from eculizumab occurred in the eculizumab arm of this study. This provides a comparison of the efficacy for the primary endpoint and clinical trial experience of the switching. This is of relevance in clinical use if patients find pegcetacoplan injections intolerable and need to return to a C3 inhibitor, or if they have an inadequate response to a C3 inhibitor and are switching to pegcetacoplan.

Neither C3 nor C5 inhibition is curative so treatment is expected to be long-term. The initial 16-week Phase III data were considered insufficient to support the registration by the evaluator and the Delegate supports this position. The Week 48 data provided at the second round of evaluation serve to reduce some of the uncertainty. The patients continuing from the run-in period, through the randomised then open label periods in this study have 52 weeks of exposure.

The primary assessment is based on haematological response. On this basis, pegcetacoplan was superior to eculizumab in haemoglobin improvement. The least square mean (LSM) difference of +3.84 g/dL is statistically and clinical meaningful. For other haematological parameters of absolute reticulocyte count (ARC) and transfusion dependence pegcetacoplan was non-inferior to eculizumab, however the difference from Baseline for lactate dehydrogenase (LDH) was not non-inferior for pegcetacoplan versus eculizumab. Although outside the testing hierarchy there was a clinically meaningful difference in FACIT-Fatigue Scale score.[20]

The evidence to Week 48 presented is indicative of a likely durable effect for haemoglobin reduction and ARC.

Although there was an improvement in haematological parameters haemolysis was reported in up to 19.5% patients (in the open label period of Study APL2-302/the PEGASUS trial).

The safety evidence to support pegcetacoplan is limited in patient numbers and to a lesser extent duration of exposure. Only 145 patients have been exposed to any dose of pegcetacoplan and 36 have been exposed for more than one year. There are therefore uncertainties in the long-term safety data set that will need to be accounted for in the post-marketing setting.

There are expected risks with complement inhibition, particularly associated with the risk of infection with encapsulated bacteria. Patients entering the study required vaccination, and a proposed boxed warning is expected to highlight this infection risk in the Empaveli Product Information. The risk of serious infection with long-term treatment is yet to be well characterised.

A notable difference between eculizumab and pegcetacoplan is injection site reactions, that may in part be due to the relatively large volume of the subcutaneous injection and in part by the presence of the polyethylene glycol in the structure of the molecule that has its own hypersensitivity concerns.

Through the risk management plan (RMP) the sponsor proposes additional pharmacovigilance and risk minimisation activities designed to collect additional data and to socialise the risks of the medicine to prescribers and to patients.

Provided this aspect is resolved it is considered in this rare disease with potentially life-threatening sequelae pegcetacoplan is another treatment option, that offers meaningful improvement in haemoglobin over the current therapy. There are uncertainties with long-term safety and longer-term efficacy has only been established in a small number of patients. If approved, the proposed dosing is 1080 mg twice weekly.

Treatment-naïve population

The indication seeks to include patients who are C5 naïve. The evidence for this subset of patients is from a single arm study data in which the dosing, while demonstrated to be similar to that proposed for registration is not the same, and there is reliance on pharmacodynamic (PD) endpoints to suggest pegcetacoplan activity in PNH that is independent of prior therapy. The evaluator has accepted this approach. In light of independent expert advice, highlighting the limitations of the data set, the Delegate has given further consideration to first-line treatment with pegcetacoplan in C5 inhibitor naïve patients.

The main data in this patient subpopulation are derived from 20 patients so the numbers of patients are too small to address key concerns such as the frequency of breakthrough haemolysis (10% based on current data), safety events such as the risk of serious infection, and other safety events because of a lack of power to detect uncommon and rare events. There are too few patients to make any meaningful assessment of whether any safety concerns are ameliorated or enhanced due to prior treatment with C5 inhibitors.

Proposed action

Paroxysmal nocturnal haemoglobinuria (PNH) is a serious, debilitating disease requiring life long treatment. It is a rare condition and small patient numbers are not unexpected in clinical trials however this limits the conclusions that can be drawn. There is sufficient evidence to support the registration of pegcetacoplan for the treatment of PNH but the most robust evidence is after treatment with eculizumab. Additional data are expected as ongoing studies mature, however based on current evidence and with the safety and efficacy uncertainties as outlined above, the further adding weight to an indication second line. It is expected this will be revisited by the sponsor in due course following the

generation of additional data to further understand potential issues such as breakthrough haemolysis, the risk of serious infection, tolerability and compliance outside a clinical trial setting.

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***The transfer device, syringe, tubing and needle sets such as 'the infusion pump and the infusion system' were not readily located on a search of the ARTG. Please provide the ARTG numbers for these devices. If they are not registered, please indicate the registered devices that are suitable for use with Empaveli.***

The sponsor advises that the following suitable devices are registered on the ARTG:[24]

- ARTG 165733 mechanically operated infusion pump
- ARTG 166653 needle, injection, single use
- ARTG 338953 multichannel general-purpose infusion pump
- ARTG 358611 electric infusion pump administration set
- ARTG 131232 infusion pump, syringe
- ARTG 325821 infusion pump, general purpose
- ARTG 325889 electric infusion pump administration set
- ARTG 325943 infusion pump, syringe

2. ***The 20 mL volume delivered subcutaneously raises concerns about the long-term tolerability of this formulation. Please comment.***

Available data indicate that pegcetacoplan administered systemically as a 20 mL subcutaneous infusion is well-tolerated over the long term. In the earlier Phases Ib and IIa studies, subjects received pegcetacoplan 180 mg, 270 mg, 360 mg, or 440 mg subcutaneously daily for up to 364 days in Studies APL2-202 and APL-CP-PNH-204 and for up to 729 days in Study APL-CP0514 before switching to twice weekly dosing. In these studies, no injection site reactions were severe, and none led to discontinuation. While local infusion site reactions may occur, data from all studies with subcutaneous administration show that these are generally mild in severity, and generally do not lead to treatment discontinuation. As of 24 September 2021, there are 253 patients who have received at least one dose of subcutaneous pegcetacoplan for a cumulative exposure of 359.3 years. In all subcutaneous administration studies, including the ongoing long-term extension Study APL2-307, 200 subjects have been exposed for more than 3 months, 186 subjects have been exposed for over 6 months, 160 subjects have been exposed for more than one year, 79 subjects have been exposed for over 2 years, and 18 subjects have been exposed for more than 3 years. Therefore, it is possible for patients to be treated long-term with a 20 mL volume of pegcetacoplan.

3. ***A number of post-marketing commitments and requirements were agreed with the United States (US) Food and Drug Administration (FDA) to support the approval of pegcetacoplan, and there is a proposal to impose those same commitments and requirements in Australia.***

[24] Details of these medical devices can be found by searching the Australian Register of Therapeutic Goods (ARTG). Available at: https://www.tga.gov.au/searching-australian-register-therapeutic-goods-artg.

a. Please provide an update on the status of those commitments, including which studies are underway and those which are no longer proposed. Please provide the expected finalisation of study reports.

The sponsor advises that the FDA commitments were to provide the following clinical study reports. The status of these studies and reports are also included below:

- Final 48-week clinical study report for Study APL2-302, a Phase III, randomised, multicentre, open label, active comparator controlled study to evaluate the efficacy and safety of pegcetacoplan in patients with PNH.

This report was provided to TGA with response to a TGA request for information.

- The final report for Study APL2-307, an open label, nonrandomised, multicentre, extension study to evaluate the long-term safety and efficacy of pegcetacoplan for the treatment of PNH in patients who have completed another pegcetacoplan clinical study.

The dates agreed with the FDA are for provision of the interim report June 2022, with trial completion August 2025 and the final report available in February 2026.

- The final report for Study APL2-308, a Phase III randomised, multicentre, open label, controlled study to evaluate the efficacy and safety of pegcetacoplan as monotherapy compared to standard of care (excluding complement inhibitors) in patients with PNH.

The dates agreed with the FDA are for provision of the final report in April 2022, with trial completion October 2021.

- The sponsor should also further develop studies to evaluate the development of anti-drug antibodies, neutralising antibodies.

The following 3 steps and timelines were agreed with the FDA:

- Develop a sensitive assay to detect and monitor the presence and titer of antibodies that bind the active moiety of pegcetacoplan. The assay should be capable of detecting neutralising anti-pegcetacoplan antibodies in the presence of pegcetacoplan levels that are expected to be present in serum at the time of patient sampling. The final report should include development and validation data to support use of the assay.
  - Draft protocol submission: July 2021
  - Final protocol submission: November 2021
  - Final report submission: May 2023
- Develop and validate a sensitive assay to evaluate the neutralising activity of anti-drug antibodies detected in patient samples. The assay should be capable of detecting neutralising anti-drug antibodies in the presence of pegcetacoplan levels that are expected to be present in serum at the time of patient sampling. The final report should include development and validation data to support use of the assay.
  - Draft protocol submission: July 2021
  - Final protocol submission: November 2021
  - Final report submission: May 2023
- Use the developed assays in Steps 1 and 2 to establish the incidence, titre, and neutralising activity of antibodies to pegcetacoplan in patient samples from Studies APL2-302, APL2-307, and APL2-308. Establish whether there is an impact of antibodies on safety and efficacy of pegcetacoplan. Submit datasets at the time of final report submission.
  - Draft protocol submission: July 2023

- Final protocol submission: November 2023
- Final report submission: August 2026

The current status of Steps 1 and 2 are that draft protocols were submitted to the FDA for review on 27 July 2021.

b. Please comment on the development of a registry to further characterise the activity of pegcetacoplan in PNH. Will Australian patients be eligible for inclusion? What type of reporting is expected from the registry and when are reports anticipated?

The sponsor does not currently intend to setup a company owned disease registry.[25] The International PNH Interest Group (IPIG) is a global professional society that focuses specifically on PNH independent from Swedish Orphan Biovitrum (Sobi). The IPIG is currently setting up a global PNH disease registry called the IPIG PNH Registry. The model of the IPIG PNH Registry is that all patients with PNH will be eligible for inclusion, regardless of where they are in the world, whether they are receiving PNH specific therapy and regardless of what type of therapy or treatment they are receiving.

The sponsor is planning to conduct an observational PASS, using safety data extracted from the IPIG PNH Registry in patients treated with pegcetacoplan. It should be noted that as such a study is only observational it will not affect the patient and investigator relationship, nor influence the investigator's drug prescription or therapeutic management of the patient. The decision to treat patients with pegcetacoplan will be independent from the decision to enrol patients in the study. The sponsor intends to include patients from Australia to participate in a PASS.

Within the IPIG PNH Registry, baseline and follow-up assessments will be performed by the treating physician according to standard of care. Patient data will be entered into the IPIG PNH Registry by the treating physician at enrolment, Month 3, Month 6, and every 6 months thereafter.

Related to data collection and reports for the observational PASS, the sponsor has proposed the following milestones (and this will be reflected in the final RMP/ASA to be submitted to TGA post-approval, that is, following approval in both Australian and the EU so that the EU-RMP will be the final approved version. This commitment was provided to the TGA on 2 September 2021)

- Start of data collection: the third and fourth quarter of 2022
- End of data collection: the fourth quarter of 2027
- Interim study reports: annually throughout the PASS
- Progress report: twice per year until the end of the study
- Final study report: less than one year after last patient, last visit

It should be noted that in EU the pegcetacoplan Marketing Authorisation Application is under review. An updated EU-RMP (version 0.3, dated 16 September 2021) has been submitted to the EMA for review, that includes an additional PASS that will focus on pregnancy and pregnancy outcomes. This proposed PASS is also observational and will also use the IPIG PNH Registry as the data source. As previously committed, the EMA approved EU-RMP, along with the appropriately updated ASA, will be submitted to the TGA once available.

[25] The statement does not reflect the current sponsor (Swedish Orphan Biovitrum Pty Ltd)'s position.

Independent expert advice

The Delegate received the following independent expert advice from two experts.

1. ***Paroxysmal nocturnal haemoglobinuria (PNH) is a condition that requires ongoing management. From a clinical perspective, does the data up to Week 48 (with up to 52 weeks in eculizumab pre-treated patients) from Study APL2-302 (the PEGASUS trial) provide sufficient evidence to support the use of this product in adult patients with PNH?***

Both experts agree the data so far are sufficient to support the use of the product in adults with PNH. Both pointed to the need for longer-term data.

Both experts pointed to uncertainties within the data set. Concerns included whether the potential for breakthrough haemolysis continues to develop over time, and the impact of anti-pegcetacoplan, or anti-PEG antibodies, and their persistence over time.

2. ***The sponsor proposes an indication that reads:***

> ***'Empaveli is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH).'***

If pegcetacoplan is approved, are there any concerns from a clinical perspective if pegcetacoplan is available for use as a first-line therapy, or should it only be available after treatment with a C5 inhibitor?

Both experts recommended the use of pegcetacoplan as second-line therapy to a C5 inhibitor.

Both experts considered the main evidence arises from a trial in patients with prior treatment on eculizumab and pointed to uncertainties in the evidence so far as additional reasons to take a cautious approach with this new therapy.

One expert noted the potential clinical advantage of administration being via subcutaneous injection was somewhat mitigated by the availability of C5 inhibitors through in-home programs. The same expert was concerned about the risk compliance outside the clinical trial setting and the potential risk of haemolysis from non-compliance.

One expert noted patients could receive open label pegcetacoplan after 16 weeks in the main study. This results in difficulty attributing the risk of serious infection to the C3 or C5 inhibitor. The expert noted about a quarter of the patients had aplastic anaemia; many of these patients will also be neutropenic, often profoundly so, and this presumably will increase the risk of developing a serious infection, even if this risk remains low, which will be difficult to see in a study that only goes for 16 or 48 weeks. No data on actual neutrophil counts are provided in the published paper or appendix, or via the sponsor in the Delegate's overview, although trial inclusion criteria stated absolute neutrophil count was required to be > 0.5 x 10^9/L.

One expert felt the lack of longer-term experience focussing on the emergence of antibodies, the potential for breakthrough haemolysis and the limited understanding of the risks of serious infections are reasons for C5 inhibitors to remain as first-line therapy for PNH.

Advisory Committee considerations[26]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

[26] The **Advisory Committee on Medicines (ACM)** provides independent medical and scientific advice to the Minister for Health and the TGA on issues relating to the safety, quality and efficacy of medicines supplied in

Proposed action (post-independent expert advice)

The Delegate proposes to approve pegcetacoplan for use in paroxysmal nocturnal haemoglobinuria.

Taking into account the advice of the independent experts, and taking into account the limitations and uncertainties within the data so far, the Delegate proposes to approve the following indication:

> *Empaveli is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have an inadequate response to, or are intolerant of, a C5 inhibitor.*

If pegcetacoplan was approved the Delegate proposes to impose the following additional conditions of registration:

> The pegcetacoplan EU-RMP (version 0.2; 23 July 2021, DLP 31 May 2020), with ASA (version 0.3, dated 26 August 2021), included with Submission PM-2020-05447-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
>
> An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
>
> Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.
>
> If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter.
>
> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the DLP for that report.

Empaveli (pegcetacoplan) is to be included in the Black Triangle Scheme. The PI and CMI for Empaveli must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

The sponsor must implement a controlled access program to mitigate the important risk of serious infection as agreed to by the TGA prior to implementation.

The sponsor must also provide the following the clinical study reports for the following studies for evaluation.

Australia including issues relating to pre-market and post-market functions for medicines. Further information can be found here: https://www.tga.gov.au/committee/advisory-committee-medicines-acm.

- The final report for Study APL2-302, a Phase III randomised, multicentre, open label, active comparator controlled study to evaluate the efficacy and safety of pegcetacoplan in patients with PNH.
- The final report for Study APL2-307, an open label, nonrandomised, multicentre, extension study to evaluate the long-term safety and efficacy of pegcetacoplan for the treatment of PNH in patients who have completed another pegcetacoplan clinical study.
- The final report for Study APL2-308, a Phase III randomised, multicentre, open label, controlled study to evaluate the efficacy and safety of pegcetacoplan as monotherapy compared to standard of care (excluding complement inhibitors) in patients with PNH.

The sponsor should also further develop studies to evaluate the development of anti-drug antibodies and/or neutralising antibodies.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Empaveli (pegcetacoplan) 1080 mg/20 mL, solution for injection, vial, indicated for:

> *Empaveli is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have an inadequate response to, or are intolerant of, a C5 inhibitor.*

Specific conditions of registration applying to these goods

- Empaveli (pegcetacoplan) is to be included in the Black Triangle Scheme. The PI and CMI for Empaveli must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The pegcetacoplan EU - risk management plan (RMP) (version 0.2; 23 July 2021, data lock point 31 May 2020), with Australian specific annex (version 0.3, dated 26 August 2021), included with Submission PM-2020-05447-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

  If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's guideline on Good Pharmacovigilance Practices (GVP) module VII-periodic safety update report ([revision] 1), part VII.B structures and

processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

- The sponsor must implement a controlled access program to mitigate the important risk of serious infection as agreed to by the TGA prior to implementation.
- [The sponsor to] provide the following the clinical study reports for the following studies for evaluation:
  - The final report for Study APL2-302, a Phase III randomised, multicentre, open label, active comparator controlled study to evaluate the efficacy and safety of pegcetacoplan in patients with paroxysmal nocturnal haemoglobinuria (PNH).
  - The final report for Study APL2-307, an open label, nonrandomised, multicentre, extension study to evaluate the long-term safety and efficacy of pegcetacoplan for the treatment of PNH in patients who have completed another pegcetacoplan clinical study.
  - The final report for Study APL2-308, a Phase III randomised, multicentre, open label, controlled study to evaluate the efficacy and safety of pegcetacoplan as monotherapy compared to standard of care (excluding complement inhibitors) in patients with PNH.
- The sponsor should also further develop studies to evaluate the development of anti-drug antibodies, and neutralising antibodies.
- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Empaveli approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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