14 October 2021
EMA/CHMP/629737/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Aspaveli

International non-proprietary name: pegcetacoplan

Procedure No. EMEA/H/C/005553/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Aspaveli
Applicant:	Swedish Orphan Biovitrum AB (publ) SE-112 76 Stockholm SWEDEN
Active substance:	Pegcetacoplan
International Non-proprietary Name/Common Name:	pegcetacoplan
Pharmaco-therapeutic group (ATC Code):	L04AA54
Therapeutic indication:	Aspaveli is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months.
Pharmaceutical form:	Solution for infusion
Strength:	1080 mg
Route of administration:	Subcutaneous use
Packaging:	vial (glass)
Package sizes:	1 vial and 8 vials

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List of abbreviations

AE adverse event

AP50 alternative complement pathway hemolytic activity

ANCOVA analysis of covariance

ARC absolute reticulocyte count

ATC Anatomical Therapeutic Class

AV atrioventricular

BLQ below limit of quantification

BMI body mass index

CBPI control-based pattern imputation

CFB change from baseline

CH50 total hemolytic complement activity assay

CSR clinical study report

CV coefficient of variation

Cys Cysteine

DMC data monitoring committee

ECG electrocardiogram

eCRF electronic case report form

ELISA Enzyme-linked immunosorbent assay

FACIT Functional Assessment of Chronic Illness Therapy

Fmoc Fluorenylmethoxycarbonyl protecting group

GC Gas Chromatography

GCP Good Clinical Practice

Hb haemoglobin

HPLC High performance liquid chromatography

HS GC-FID Headspace gas chromatography with flame ionization detection

IC Ion chromatography

ICE intercurrent event

ICF informed consent form

ICH International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ISR injection site reaction

ITT intention-to-treat

KF Karl Fischer titration

LASA Linear Analog Scale Assessment

LDH lactate dehydrogenase2;é;

LDPE Low density polyethylene

LS least-square

MALDI-TOF-MS Matrix-assisted laser desorption/ionization - time of flight mass spectrometry

MedDRA Medical Dictionary for Regulatory Activities

mITT modified ITT set

MMRM mixed-effect model for repeated measures

NIM noninferiority margin

NMT Not more than

PD pharmacodynamic

PDE Permitted Daily Exposure

PEG polyethylene glycol

Ph. Eur. European Pharmacopoeia

PI principal investigator

PK pharmacokinetic

PP per-protocol

PRBC packed red blood cell

PT preferred term

QoL quality of life

QLQ-C30 European Organisation for Research and Treatment of Cancer

Quality of Life Questionnaire–Core 30 Scale

QTc corrected QT interval

QTcB QT interval corrected for heart rate using Bazett’s formula

QTcF QT interval corrected for heart rate using Fridericia’s formula

RBC red blood cell

RCP randomized controlled period

RP-HPLC Reversed-phase HPLC

SAE serious adverse event

SAP statistical analysis plan

SC subcutaneous

SEC-MALS Size-exclusion chromatography - multiangle light scattering

SE-HPLC Size exclusion HPLC

SmPC Summary of Product Characteristics

SOC system organ class

SPPS Solid-Phase Peptide Synthesis

TEAE treatment-emergent adverse event

TAMC Total Aerobic Microbial Count

TYMC Total Combined Yeasts/Moulds Count

ULN upper limit of normal

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Swedish Orphan Biovitrum AB (publ) submitted on 10 September 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Aspaveli, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 January 2020.

Aspaveli, was designated as an orphan medicinal product EU/3/17/1873 on 22 May 2017 in the following condition: Treatment of paroxysmal nocturnal haemoglobinuria.

The applicant applied for the following indication treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) previously treated with standard therapy.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Aspaveli as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: ema.europa.eu/en/medicines/human/EPAR/Aspaveli

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0149/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0149/2020 was not yet completed as some measures were deferred.

The PDCO issued an opinion on compliance for the PIP EMEA-C1-002600-PIP01-19.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. New active Substance status

The applicant requested the active substance pegcetacoplan contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
14 September 2017	EMEA/H/SA/3633/1/2017/PA/SME/III	Dr Hrefna Gudmundsdottir, Dr Armando Magrelli
22 February 2018	EMEA/H/SA/3633/1/FU/1/2017/PA/SME/II	Dr Hrefna Gudmundsdottir, Prof. Brigitte Bloechl-Daum

The applicant received Protocol Assistance on two occasions as mentioned in the table above for the development of pegcetacoplan for treatment of PNH. The Protocol Assistance pertained to the following Quality, Pre-Clinical and Clinical aspects:

- Designation of starting materials
- Drug substance specifications
- Comparability of starting material sourced from different suppliers
- Drug product release specifications and stability characterisation
- New formulation for introduction in phase 3 study
- Overall pre-clinical pharmacology and toxicology strategy
- Change from sc bolus to sc infusion injection
- Unmet medical need
- Phase 3 study design: study population, placebo control, background therapy, adjunctive therapy to eculizumab and options to investigate reduction in eculizumab requirements, primary and secondary efficacy endpoints, dosing regimen, statistical analysis plan, appropriateness as single pivotal study
- Safety database, with a focus on the characterisation of cardiac safety
- Evidence to support the maintenance of significant benefit for orphan designation

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: Selma Arapovic Dzakula

The application was received by the EMA on	10 September 2020
The procedure started on	1 October 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 December 2020

The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	22 December 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	5 January 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 January 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 April 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	02 June 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 June 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	24 June 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	16 August 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	3 September 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	16 September 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 September 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 September 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Aspaveli on	14 October 2021
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	14 October 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

PNH is a rare, chronic, life-threatening blood disorder associated with anemia due to hemolysis. Hemolysis can result in a range of debilitating consequences such as severe fatigue, chest pain, and transfusion dependence, all of which contribute to the heavy disease burden and reduced quality of life (QoL) these patients experience. Even with C5 inhibitor treatment, 72% of patients with PNH remain anemic and 36% require 1 or more transfusions per year (McKinley et al. 2017). If left untreated, PNH can cause severe and potentially fatal complications for patients.

2.1.2. Epidemiology

PNH has an annual incidence of 1-10 new cases per 1 million individuals. The median age of diagnosis is in the early thirties; it affects men and women in equal proportions and has no clear ethnic or geographic preferences (Stern and Connell 2019).

2.1.3. Aetiology and pathogenesis

PNH is characterized by chronic complement-mediated hemolysis, which most commonly occurs as a consequence of a somatic mutation in the phosphatidylinositol glycan class A (PIGA) gene. This genetic mutation causes impaired glycosylphosphatidylinositol (GPI) biosynthesis and deficient GPI-anchored complement regulatory proteins on the surface of mature blood cells, rendering these cells susceptible to complement attack (Schrezenmeier et al. 2020).

2.1.4. Clinical presentation and diagnosis

PNH is associated with a high burden of disease. The most prevalent symptoms are fatigue (80%), dyspnea (64%), and hemoglobinuria (62%). PNH commonly results in clinically significant hematologic consequences from chronic hemolysis including a marked increase in risk of thromboembolism, which may ultimately lead to target organ damage and death (Schrezenmeier et al. 2014).

2.1.5. Management

To most effectively manage PNH, both IVH and EVH need to be controlled. This is reflected in improvements across the following key markers of disease activity: hemoglobin level, LDH level, ARC, bilirubin level, transfusion requirements, and FACIT-Fatigue score. The C5 inhibitors eculizumab and ravulizumab, the only currently available treatments, have increased survival and improved outcomes in PNH by controlling IVH, reflected in LDH improvements; however, C5 inhibitors do not control EVH. In many patients treated with C5 inhibitors, although LDH is largely controlled, ARC and bilirubin levels remain elevated, indicative of ongoing hemolysis. Despite the availability of eculizumab over the past 13 years, patients remain symptomatically limited by their disease and still require PRBC transfusion because not all key markers of disease activity are meaningfully improved. Considering the available therapies, there is no unmet medical need. However, new therapies that provide more complete control are needed.

2.2. About the product

Pegcetacoplan is formed by a pentadecapeptide (combining a bioactive cyclic tridecapeptide C3-inhibiting moiety and a 2–amino acid linker) covalently coupled to each end of a linear 40-kDa polyethylene glycol (PEG) chain, so there are 2 peptide moieties per molecule of pegcetacoplan.

Pegcetacoplan (Pharmacotherapeutic group: Selective immunosuppressants) binds to complement protein C3 and its activation fragment C3b with high affinity, thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation.

The claimed indication is treatment of paroxysmal nocturnal haemoglobinuria (PNH) in adult patients that have previously received standard therapy haemoglobinuria.

Pegcetacoplan is administered twice weekly as a 1,080 mg subcutaneous infusion with a commercially available syringe system infusion pump. The twice weekly dose should be administered on day 1 and day 4 of each treatment week. For the first 4 weeks, pegcetacoplan is administered as twice weekly subcutaneous doses of 1,080 mg in addition to the patient's current dose of C5 inhibitor treatment to minimize the risk of haemolysis with abrupt treatment discontinuation. After 4 weeks, the patient should discontinue C5 inhibitor before continuing on monotherapy with pegcetacoplan.

Before receiving treatment with pegcetacoplan,in patients with a known history of vaccination, it is recommended to ensure that patients have received vaccines against encapsulated bacteria including Streptococcus pneumoniae, Neisseria meningitidis types A, C, W, Y, and B, and Haemophilus influenzae Type B (Hib) within 2 years prior to starting Pegcetacoplan. For patients without known history of vaccination, it is recommended to administer the required vaccines at least 2 weeks prior to receiving the first dose of pegcetacoplan. If immediate therapy with pegcetacoplan is indicated, it is recommended to administer required vaccine as soon as possible and provide patients with 2 weeks of prophylactic antibiotic therapy.

2.3. Type of Application and aspects on development

Early clinical evaluation (CP0514, 204, 202 studies) of repeated dosing of pegcetacoplan in subjects with PNH was conducted, and pegcetacoplan demonstrated pharmacological activity at an SC dosage of 180 mg/day, but an improved efficacy response was observed at an SC dosage of 270 to 360 mg/day. On the basis of the efficacy observed in the Phase 1b/2a clinical trials and to reduce the burden of daily dosing, a twice-weekly dose of 1080 mg by SC infusion was selected for pivotal Phase 3 ongoing APL2-302 study on the basis of preliminary pharmacokinetic (PK) modelling.

Others phase 3 studies are ongoing: the extension APL2-307 study and APL2-308 study assessing efficacy and safety of pegcetacoplan in patients with PNH compared to standard of care excluding complement inhibitors.

On 12 June 2017 the Applicant requested protocol assistance (EMA/CHMP/SAWP/579653/2017) for APL-2-301 study assessing patients receiving 270 mg/day of pegcetacoplan in order to support the indication for the treatment of patients with PNH with inadequate response to eculizumab. As the Applicant was not planning to conduct the APL2-301 protocol, a further follow up advice was requested on 6 November 2017 (EMA/CHMP/SAWP/100648/2018) for APL2-302 study. The study design was generally agreed upon. However, it was recommended to extend the active-comparator controlled period to provide more long-term data on the endpoints of interest. This recommendation was not followed by the Applicant, however, efficacy and safety data beyond the controlled period have been submitted from an open label period.

The Applicant was advised to randomise before run-in and not afterwards and to blind the study (using a "double-dummy" design) to minimise the risk of bias with open label design. This advice was also not adhered to, however, the applicant submitted an exhaustive argumentation to address the CHMP concerns regarding the study design.

The application included an EMA Decision(s) EMEA-002600-PIP01-19 on the agreement of a paediatric investigation plan P/0149/2020. The clinical measures were the following studies:

- Study 1 (APL2-PNH-209): Open label, multiple dose trial to evaluate pharmacokinetics, safety and activity of pegcetacoplan in children from 12 to less than 18 years of age with anaemia due to PNH who are treatment naive or who remain anaemic despite treatment with a complement inhibitor. The study initiation and completion is deferred with the date of completion due by April 2024.

- Study 2 (APL2-PNH-003): Use of population PK model to analyse PK data collected in paediatric studies to inform dosing recommendation in paediatric subjects. The initial population modelling analysis report is available and has been provided with the compliance check package. Thus, the date of initiation of study 2 is compliant. The completion of this measure is deferred with completion expected by September 2024.

- Study 3 (APL2-PNH-004): Use of population PK/PD and E-R model of existing in-house clinical data on pegcetacoplan to support efficacy assumptions in the paediatric population based on extrapolation. The study initiation and completion are deferred with the date of completion due by April 2024.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a solution for infusion containing 1080 mg of pegcetacoplan as active substance (in a 20 mL vial). Each mL of solution contains 54 mg of pegcetacoplan.

Other ingredients are: sorbitol (E420), glacial acetic acid, sodium acetate trihydrate, sodium hydroxide (for pH adjustment) and water for injection.

The product is available in a type I glass vial with a stopper (cholorobutyl) and a seal (aluminium) with a flip-off cap (polypropylene) as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

Pegcetacoplan is a synthetic molecule comprised of two identical peptides covalently linked to both ends of a linear 40 kDa polyethylene glycol (PEG) in a site-specific manner.

The chemical name of pegcetacoplan is *N*6,15,*N*6,15'-[poly(oxyethylene), oxy-α-carbonyl, ω-carbonyl]-bis[*N*-acetyl-L-isoleucyl-L-cysteinyl–L-valyl–1-methyl-L-tryptophyl-L-glutaminyl–L-aspartyl–L-tryptophylglycyl-L-alanyl-L-histidyl–L-arginyl–L-cysteinyl–L-threonyl–2-[2-(2-aminoethoxy)ethoxy]acetyl-L-lysinamide, cyclic (2-12)-disulfide] corresponding to the molecular formula $C_{1970}H_{3848}N_{50}O_{947}S_4$. It has a relative molecular mass 43.5 kDa and the following structure:

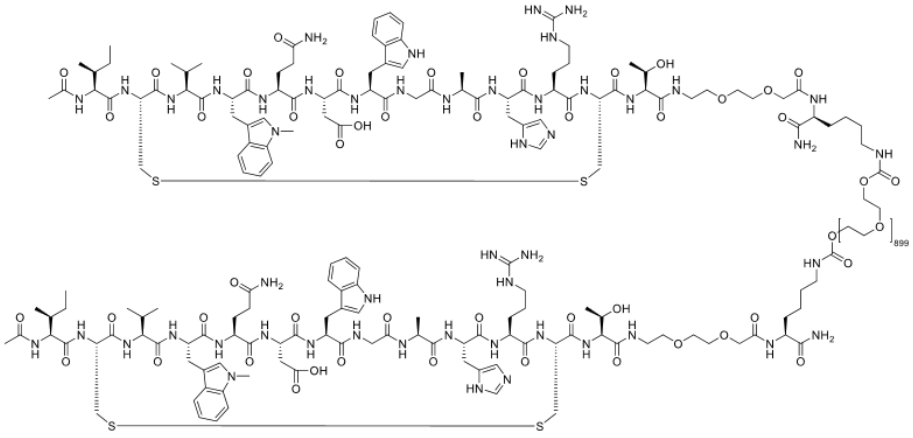


Figure 1: active substance structure

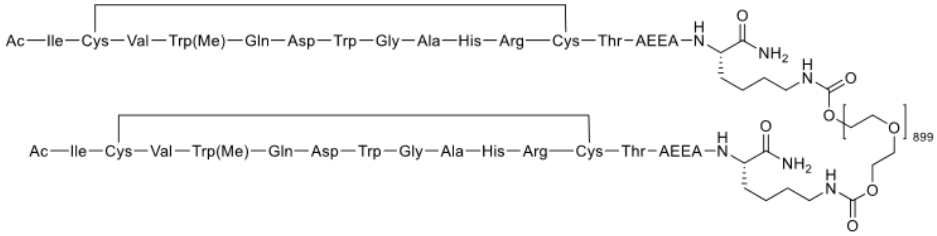


Figure 2: active substance structure using peptide abbreviations

A broad set of analytical methods have been used to elucidate the structure of the active substance and characterise it. This includes i) structural studies, including route of synthesis analysis, sequencing, peptide mapping, circular dichroism, molecular weight determination by MALDI-TOF-MS, molecular weight/polydispersity/molecular weight distribution by SEC-MALS, amino acid analysis, ^{1}H-NMR, FT-IR, UV/Vis spectroscopy, combustion analysis, chiral amino acid analysis, and disulphide bonding; ii) physicochemical characteristics, including appearance, solubility profile, optical rotation, analysis of thermal properties by differential scanning calorimetry, thermogravimetric analysis, isoelectric point, pH in solution, molar extinction coefficient, solid-state properties by X-ray powder diffraction, hygroscopicity, and residue on ignition; iii) purity and impurity tests, including three orthogonal HPLC methods (reversed phase (RP)-, size exclusion (SE)-, and strong cation exchange (SCX)-HPLC), analytical ultracentrifugation, acetate content, and free-PEG content; vi) biophysical and biological attributes, including biopotency by ELISA and thermodynamic properties by isothermal calorimetry.

The active substance is a white to off-white solid, very soluble in both water and buffer (10 mM acetate buffer, pH 5.0 containing 4.1% sorbitol), and freely soluble in both ethanol and 5% dextrose solution. At 25 °C, pegcetacoplan displays negligible adsorption of water at moderate relative humidity (RH) levels (less than 3% water adsorption at RH ≤ 65%) and low to moderate water adsorption at high relative humidity levels (~6% water adsorption at 85% RH).

All the chiral amino acids contain the L configuration. The peptide portions contain two unnatural amino acids: 1-methyl-L-tryptophan (Trp(Me)) in position 4 and amino(ethoxyethoxy)acetic acid (AEEA) in position 14. The polyethylene glycol bridging the two peptides consists of 900 repeating units representing a nominal mass of 40 kDa and is covalently linked to the side chains of each lysine residue of each peptide.

The crystallinity of the active substance is not critical to the bioavailability of the finished product since the product is administered as a solution for infusion. Hence the absence of polymorphism discussion in the dossier is acceptable.

2.4.2.2. Manufacture, characterisation and process controls

The manufacture of the active substance consists of eight specific stages.

The starting materials are Rink Amide AM Resin, the protected amino acids and PEG Diol (40K) and they are considered acceptable with acceptable specifications. The starting materials are commercially available.

A detailed description of each stage of the manufacturing process is provided. Critical process parameters (CPP) and their proven acceptable ranges are described. In-process tests are listed for each stage of the manufacturing process.

The process description provided by the applicant is very detailed and consistent with standard chemistry and controls for SPPS. This high level of detail provides a large degree of assurance that the process will be under sufficient control. Critical steps and controls have been identified and the designation of them as critical/non-critical is acceptable based on the multiple chromatographic purification steps used in the process. Holding times and storage conditions for process intermediates were established based on data generated during development, stability studies, and/or manufacturing experience and are acceptable.

In-process controls applied during the synthesis are described. The specifications and control methods for critical steps, intermediate products, starting materials and reagents have been presented.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified.

Potential and actual impurities are described in detail. A detailed summary of the genotoxic assessment performed for each pegcetacoplan manufacturing process reagent, solvent, and potential by-products, raw materials and intermediates produced during manufacturing of the activated PEG intermediate and the peptide intermediate is provided. All compounds were classified either as ICH M7 class 5 or as ICHQ3C class 2 except for acetamide for which a PDE is established.

The active substance is packaged in an LDPE bag which complies with the European Union Regulations EU/10/2011, and EC/1935/2004. The secondary packaging is an opaque aluminium-lined laminate bag that provides protection from light.

2.4.2.3. Specification

The active substance specification includes tests for appearance (visual), identification (MALDI-TOF-MS and RP-HPLC), assay (RP-HPLC), purity (RP-HPLC), related substances (RP-HPLC, SE-HPLC, SEX-HPLC), water content (KF), residual organic solvents (HS GC-FID), acetate content (IC), bioassay (ELISA), bacterial endotoxins (Ph. Eur.) and microbial enumeration (Ph. Eur.).

The applicant has provided a detailed and sound justification of the proposed limits in line with ICH Q6A. An acceptable toxicological justification has been provided for those impurities where the respective limit is above the Ph. Eur. qualification threshold (1.0%).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for 11 process validation and post process validation batches of the active substance have been provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from three batches of active substance from the proposed active substance manufacturer stored in a container closure system representative of that intended for the market for up to 18 months under long term conditions (- 20°C ± 5 °C) and for up to 6 months under accelerated conditions (5 ± 3°C) according to the ICH guidelines were provided. Two of these batches were manufactured at the proposed commercial size while one batch was approximately one half of the commercial size. For these three batches, the activated PEG intermediate used to produce the active substance was manufactured at pilot scale by the site of manufacture for this intermediate used during development. The use of batches with intermediate from this site is acceptable based on the comparability data provided.

The following parameters were tested*:* appearance, assay, purity, related substances, water content, impurities, bioassay, bacterial endotoxins and microbial enumeration. The analytical methods used were stability indicating. All tested parameters were within the specifications.

The PEG intermediate manufacturing process was scaled up at the site proposed for commercial manufacturing. Stability data are available for four additional active substance lots using PEG intermediate from this site. To date, stability data through 12-months at the long-term and 6-months under the accelerated condition are available. No significant trends were observed, and the tested samples met the proposed commercial active substance specification. The results from these studies support the comparability assessment.

Forced degradation studies were conducted and pegcetacoplan was exposed to thermal, aqueous hydrolytic, acidic, basic, and oxidative stress conditions. Results of these studies showed that pegcetacoplan is susceptible to degradation under aqueous hydrolytic, acidic, basic, and peroxide oxidative conditions. No significant change in purity and related impurities by RP-HPLC was observed in pegcetacoplan samples exposed to thermal stress conditions.

Photostability testing following ICH guideline Q1B was performed on one batch. The photostability characteristics of pegcetacoplan were evaluated by exposing the active substance and a dark control to light conditions that meet or exceed the conditions for confirmatory studies specified in ICH Q1B, Section 1B Option 1. Samples were tested for appearance, appearance of solution, purity and related substances (RP-HPLC, SE-HPLC, SCX-HPLC) and bioassay. The data indicate that there is no change in the colour and physical form of the exposed samples. In addition, no change was observed in the clarity or colour of a sample solution. No visible impurities were observed in any of the samples. The data show a significant decrease in the purity accompanied by an increase in impurities. A decrease in bioassay is also observed. Therefore, it can be concluded that pegcetacoplan shows significant sensitivity to visible and/or UV light exposure.

The proposed 18-month retest period for pegcetacoplan stored at -20 ± 5°C (-20°C) protected from light is considered acceptable. The available accelerated stability data (6 months at 5°C) support short-term excursions outside the proposed label storage condition of -20°C during handling.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Pegcetacoplan solution for subcutaneous infusion, 1080 mg is a sterile aqueous, acetate-buffered sorbitol solution for parenteral administration.

The qualitative composition of the finished product is presented in the table below:

Table 1: composition of the finished product

Ingredient	Quality Standard	Function
Pegcetacoplan	In-house standard	Drug substance
Sorbitol	NF/Ph.Eur./JP	Tonicity agent
Glacial acetic acid	USP/Ph.Eur./JP	Buffering agent
Sodium acetate trihydrate	USP/Ph.Eur./JP	Buffering agent
Sodium hydroxide	NF/Ph.Eur./JP	pH adjustment
Glacial acetic acid	USP/Ph.Eur./JP	pH adjustment
Water for injection	USP/Ph.Eur./JP	Solvent

No overages are used in the pegcetacoplan finished product formulation, however an overfill is used. An acceptable justification for the overfill volume has been provided.

The active substance concentration was set to deliver the required amount (1080 mg) in a 20 mL infusion dosage form. The active substance, pegcetacoplan, is is a symmetrical molecule comprised of two pentadecapeptides covalently bound to the ends of a linear 40 kDa polyethylene glycol molecule. The active substance is a lyophilized amorphous solid of low bulk density which is freely soluble to very soluble in aqueous solutions. Consequently, there are no risks to achieve complete dissolution to a final concentration of 54 mg/mL during finished product manufacturing.

The list of excipients is included in section 6.1 of the SmPC. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The excipients and the quantities used are common in the manufacture of this type of dosage form and considered safe in the proposed concentrations. Their functions are adequately described. Sorbitol is used as a tonicity agent. Glacial acetic acid is used as a buffering agent and for pH adjustment. Sodium acetate trihydrate is used as a buffering agent. Sodium hydroxide is used for pH adjustment and water is used as solvent. Excipients were selected based on the route of administration and the need to stabilize the active substance in solution. Acetate buffer was selected based on the pH of optimal stability of the active substance, which is within an acceptable pH range known for subcutaneous administration. The buffer concentration of 10 mM acetate is adequate to maintain the pH over the proposed shelf life of the product.

Data from the different formulation development studies demonstrate the compatibility of pegcetacoplan with the selected excipients.

The formulation includes sorbitol. The concentration of sorbitol (4.1% w/v) was selected to afford an isotonic finished product. This is an excipient with known effect covered by the Excipients Guideline and included in the 'Annex to the European Commission guideline on '*Excipients in the labelling and*

package leaflet of medicinal products for human use' (SANTE-2017-11668)' (EMA/CHMP/302620/2017). This is adequately addressed in the SmPC.

Detailed information on formulation development has been presented.

An evaluation of formulations through comparison and analyses of results across studies demonstrated that there were no meaningful differences of the overall absorption and disposition profile of pegcetacoplan between the final formulation and earlier formulations.

Information on the development of the manufacturing process for the finished product has been presented.

A non-ionic tonicity agent (sorbitol) was selected for the formulation.

Pegcetacoplan is an inhibitor of the complement protein C3, and the mode of action is described in detail in relevant sections of the dossier. A biologically relevant ELISA-based assay was developed to evaluate pegcetacoplan biopotency. Bioassay data shows that the biological activity of the finished product remains stable during manufacturing and long-term storage.

The intended commercial manufacturing process, product compatibility with manufacturing components, manufacturing process characterisation, justification for critical/non-critical process parameters and in-process controls, risk assessment of the finished product manufacturing process and intended control strategy for the manufacturing process are described.

The primary packaging is a type I glass vial with a stopper (cholorobutyl), and a seal (aluminium) with a flip-off cap (polypropylene). The material complies with Ph. Eur. 3.2.1 (glass vials) and Ph. Eur. 3.2.9 (rubber stoppers) requirements.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of four main steps: 1. Compounding, 2. initial buffer preparation, 3. addition of the active substance, 4. buffer preparation/addition/mixing, pre-filtration, sterile filtration, aseptic filling and stoppering. The process is considered to be a non-standard manufacturing process due to the use of aseptic techniques (sterile filtration).

The manufacturing process has been adequately described. Adequate justification for holding times has been provided.

The chosen sterilisation method is acceptable.

During the procedure, a major objection was raised in relation to the lack of full production scale validation data for the actual sterilisation process. In response. satisfactory data from 3 production scale batches was provided demonstrating the validation of the process steps.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls and critical process parameters are adequate for this type of manufacturing process and pharmaceutical form.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual, colour, Ph. Eur.), identity (RP-HPLC, SE-HPLC), assay (RP-HPLC), degradation products (RP-HPLC, SE-HPLC, SCX-HPLC), impurities (RP-HPLC), particulate matter (Ph. Eur.), container content for injection (Ph. Eur.), pH (Ph. Eur.), osmolality (vapor pressure), bioassay (ELISA), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.).

A justification was provided for each of the proposed specification limits for degradation products which are based on ICH Q6A requirements and batch analysis data as well as stability data. The control strategy for specified degradation products is well discussed. The proposed limits for each unspecified finished product degradant are the same as in the active substance.

The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Testing for elemental impurities in the finished product has been conducted in accordance with ICH Q3D (R1) Elemental Impurities for parenteral products. Thus, Class 1 and 2A elements were included and Class 2B testing was omitted since none were used in the manufacturing process. In addition, the three Class 3 elements with the lowest permissible exposure limits were included (i.e., Cu, Sb, and Li). Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification.

During the procedure, a major objection was raised in relation to the requirement to provide a risk evaluation concerning the presence of nitrosamine impurities in the finished product. In response, the risk evaluation was performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Batch analysis results are provided for 3 production scale batches of the finished product. Additional batch analysis results were also provided for pegcetacoplan finished product batches used in clinical studies and in registration stability studies. The results provided confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from three pilot-scale batches of finished product stored for up to 18 months under long term conditions (5°C ± 3°C) and for up to 6 months under accelerated conditions (25°C / 60% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing, manufactured using the intended commercial process and formulation, and were packed in the primary packaging proposed for marketing. The stability studies were performed for vials stored in both upright and inverted orientation. The active substance lots used to manufacture the finished product registration stability batches were manufactured at commercial scale by the commercial manufacturer. The activated PEG intermediate used to produce those active substance batches was manufactured at pilot scale by the site of manufacture for this intermediate used during development. Samples were tested for appearance, identity, assay, degradation products, impurities, bioassay, particulate matter, pH, container closure integrity and sterility. The analytical procedures used are stability indicating.

Three months of long-term and 6 months accelerated stability data were also provided for an additional production-scale finished product batch using the intended commercial process and formulation. The

active substance lots used to produce the supportive finished product stability batch were manufactured using PEG intermediate from the intended commercial manufacturer.

Under long-term storage conditions, the product remained stable and tested parameters remained within specification. Under accelerated storage conditions, significant changes were observed. No noticeable differences in stability results of the finished product in upright and inverted position were observed. This confirms the suitability of the proposed primary packaging concept.

Forced degradation studies were conducted and the finished product was exposed to thermal, UV-A and visible light, acidic, basic and oxidative aqueous stress conditions and the results showed that the finished product is susceptible to degradation upon exposure to heat, base, peroxide, UV, and visible light stress conditions.

The photostability of the finished product was evaluated by exposing finished product stored in the immediate pack (consisting of a vial and stopper) and in the secondary pack (consisting of a carton) and control samples to light conditions that meet or exceed the conditions for confirmatory studies specified in ICH Q1B, Option 2. The finished product in immediate pack shows sensitivity to visible and UV light degradation while the secondary packaging provides adequate protection from light.

Based on available stability data, the proposed shelf-life of 18 months and the special precautions for storage "store in a refrigerator (2°C – 8°C) and store in the original carton to protect from light" as stated in the SmPC (section 6.3) are acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The active substance is a symmetric polypeptide covalently linked to polyethylene glycol and is manufactured via solid-phase peptide synthesis. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. During the procedure major objections were raised in relation to the finished product regarding the lack of commercial scale process validation data and the absence of a nitrosamine risk evaluation. On both questions, satisfactory responses were received to resolve the major objections.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Pegcetacoplan is constituted of two amino acid cyclic peptides conjugated to a linear polyethylene glycol (PEG) chain. The peptidic domains of the molecule are a derivative of Compostatin (a cyclic tridecapeptide with a highly potent and selective C3 inhibitory activity) and have been shown to bind C3 and C3b, resulting in inhibition of complement activation. The inhibition of C3 and C3b will have consequences on all complement system function such as opsonisation and inflammation principally.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

From the *in vitro* pharmacology studies, Pegcetacoplan was shown a binding to C3 and C3b with affinity of 15nM and 21,3 nM respectively. The EC50 of APL1 (non-pegylated peptide sequence) and pegcetacoplan seem to be similar (EC50 APL1 = 0.1648 µM and EC50 Pegcetacoplan = 0.05695 µM). The inhibitory activity of Pegcetacoplan is comparable to the non-pegylated peptide sequence demonstrating that the binding activity is little related to pegylated.

Pegcetacoplan inhibited classical and alternative activation pathways but in different manner according to species: the inhibition is significant in the serum of humans and *Cynomolgus* monkeys but there is no inhibition in serum of rabbit or rat. The animal model *Cynomolgus* Monkeys is then considered as relevant.

From the *in vivo* pharmacology studies, the highest dose of pegcetacoplan was obtained 8 hours after the day 2 and the concentration slowly declined through day 15 (end of study). To evaluate the efficacy of pegcetacoplan, the inhibition of complement system and the haemolysis activity have been measured by AH50 and CH50. AH50 and CH50 assays are traditional assays based on their lysis of antibody-coated sheep red blood cells (CH50) or rabbit red blood cells (AH50) due to activation of complement on the cell's surface. The CH50 and AH50 (50% complement Haemolytic dose Alternative Complement haemolytic dose) were determinate by adding a limiting amount of the test serum or plasma. This functional assay measured the amount of hemoglobin that was released when the target cells were lysed by the action of complement, and from this, the percentage of the cells that had been lysed was calculated (Ricklin, 2017).

At dose of 84mg/kg twice daily during 60min as intravenous injection at day 1 and day 2, Pegcetacoplan inhibited rapidly AH50 and CH50 hemolytic activity. Furthermore, the C3a and C3 levels decreased during the first 48hours (correlated with pegcetacoplan injection) and decreases of AH50 and C3a levels were also correlated with pegcetacoplan concentration. The inhibition of both classical and alternative pathways was observed in Monkeys but from the fifth day, the CH50, AH50 and C3 levels returned towards baseline. The effects on hemolysis activity, induced by the inhibition on complement, correlated with the pegcetacoplan concentration. Additionally, the Applicant discussed the scopes of pharmacological studies 18XTPH-001 and 19CFPH-001 more thoroughly as both C3 and C5 inhibitors target complement system.

2.5.2.2. Secondary pharmacodynamic studies

The secondary or off target pharmacology has not been specifically investigated considering that the peptidic domains of the molecule are a derivative of Compstatin and the PEG moiety is known to be

biologically inert. However, even if the PEG part of pegcetacoplan is biologically inert, the active part is unknown and the information provided about Compstatin is insufficient to evaluate the secondary pharmacology of pegcetacoplan. Therefore, the Applicant provided data on the potential off-target pharmacology by comparing peptide sequences of pegcetacoplan and 460 million sequences to identify sequence similarities with existing proteins or peptides that could indicate a risk of cross-reactivity or biological interactions. The data revealed no similarity in proteins or peptide sequences, natural or artificial, in humans or otherwise, supporting a low probability for cross-reactivity of pegcetacoplan against natural receptors or ligands.

2.5.2.3. Safety pharmacology programme

Several cardiac and respiratory endpoints in the toxicological studies were evaluated for safety pharmacology. Up to 300µM, there was little to no reduction in hERG current amplitude without or with Human Serum Albumin. The *in vivo* cardiac and respiratory potentials were evaluated from the toxicological study in *Cynomolgus* Monkeys (13CATX-005) after Single SC administration of pegcetacoplan (up to 140mg/kg) or PEG 40 (at 112mg/kg). No effects on body temperature, hemodynamics, electrocardiographic or respiratory parameters were observed. According to ICH M3 guidelines, several endpoints such as the tidal volume, respiratory rate or hemoglobin oxygen saturation should be measured from the toxicological studies. In study 13CATX-005, the respiratory volume and the tidal volume were assessed.

Pegcetacoplan distribution in brain was quantified in primates (Study 17MTX00001) with value below the limit of quantification. Moreover, pegcetacoplan does not cross the blood brain barrier and clinical observation did not suggest any behaviour trouble related to impairment of CNS.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interactions study has been conducted to date. Data obtained from pharmacokinetic study did not suggest major interaction between cytochrome P450 enzyme or drug transporter and pegcetacoplan.

It should be noted that pegcetacoplan will be co-administrated with eculizumab to avoid the risk of hemolysis. The AH50 values of subjects from Studies CP0514 and APL2-302 increased toward normal, reflecting persistent, partial, inhibition of the alternative pathway of complement pathway with repeated SC dosing of pegcetacoplan. The interaction between pegcetacoplan and eculizumab was evaluated as part of the PopPK analysis when co-administered to PNH subjects (studies APL2-302 and CP0514). It is expected that pharmacodynamic interactions between C3 and C5 inhibitors are very unlikely since both inhibit different parts of the complement cascade.

2.5.3. Pharmacokinetics

The LC-MS/MS assays for the measurement of pegcetacoplan have been validated adequately in rabbit and monkeys studies. The computer software to determine the TK parameters has been validated adequately. The LLOQ determined for each analysis methods is acceptable. According to Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**), the information related to analytical methods is acceptable.

Absorption

Pharmacokinetic *in vivo* analysis of pegcetacoplan in *Cynomolgus* Monkeys following a single intravenous or single or repeated dose subcutaneous administrations showed systemic exposure for all animals.

From 13APK-001 study, after a single IV or SC dose of 7mg/kg, the Cmax was achieved 212 µg/ml after 5 minutes post dose (tmax) and 105 µg/ml after 3 days post dose , followed by a gradual decline to the final timepoint on Day 15. The T1/2 was of 7.8 and 7 ,5 days respectively. The bioavailability SC was estimated to be superior to 85%. In comparison IV and SC, the mean AUC 0-last, the mean clearance and the mean Vz were similar: 1174 and 1011 µg.day/mL, 4.31 and 4.80 mL/day/kg, and 48.5 and 52.1 mL/kg respectively. After 7 consecutive daily dose at 7 mg/kg, the pharmacokinetic parameters are superior compare to single SC dose. The median Tmax was 7days, the Cmax and AUC 0-last were 558 mg/ml and 5275 µg.day/mL (5-fold to Mean cmax and AUC in single dose study). Also, the mean T1/2 was longer with 8.66days than IV route. However, the clearance and the Vz were similar to single dose study with mean clearance of 4.5mL/d/kg and a mean Vz of 50 mL/kg.

The 16CATX-003 study in 6 *Cynomolgus* monkeys females (n=3/group) compared two formulations: dextrose 5% and 0,9%NaCl + 10mM Sodium acetate trihydrate, pH 5.0. They received two consecutive daily 84 mg/kg pegcetacoplan doses administered as a 60-minute IV infusion. Pegcetacoplan was rapidly absorbed in 1.38 days (Median Tmax), with peak serum pegcetacoplan concentrations of 1805µg/mL for 5% dextrose and 1680µg/ml for 10mM acetate-buffered saline, pH 5, with an apparent t1/2 of approximately 6.68 days for both formulations. The mean AUC 0-last was 9779 and 9774 µg/day/mL respectively. There is no major difference between two formulations at 84mg/kg.

The 19CAPK-001 study in *Cynomolgus* monkeys male compared 3 different weights of pegcetacoplan formulated in Dextrose 5%: 40.3, 45.3 and 47.8 kDa after SC injection single dose of 7mg/kg. The renal clearance is mainly correlated to molecular weight and the modification pharmacokinetic parameters should be expected. The results showed no significant difference between the 3 groups: the Tmax ranged from 2.67 to 3.67 days, the mean Cmax ranged from 93.8 to 99.2 µg/mL, the AUC 0-last ranged from 963 to 1038 µg.day/mL, the mean T1/2 ranged from 7.71 to 9.71 days.

The studies 13APK-001 (Monkey female) and 19CAPK-001 (Monkey male) were comparable and showed no significant difference between all pharmacokinetic parameters and similarity between different lots of comparable molecular weights used.

Distribution

A single dose radiolabelled study in males Monkeys was conducted to evaluate the distribution of pegcetacoplan in different tissues. Radiolabeled pegcetacoplan was widely absorbed after SC administration. The peak concentration was reached at 48 hours and the concentrations were measured at different time points: 8, 72, 168, 336 and 504h. For the majority of tissues analyzed, the Cmax was obtained after 72hours (for 19 tissues of 37). With a LLOQ of approximately 153ng.equiv/g, no distribution was observed or below the limit of quantification in the brain (including cerebellum, cerebrum, medulla, and spinal cord), gastrointestinal contents and optic nerve. It should be noted that distribution in eye was observed at 8 hours but decreased after 108h (4.5 days). One subject had a mild visual impairment/intermittent visual disturbance treatment-emergent adverse event (TEAE) during the run-in phase. This adverse event was considered mild and assessed by the investigator as possibly related to pegcetacoplan. From non clinical point of view, the distribution in eyes is decreasing and at 8 hours the value wad 1/240the the value measured in plasma. Moreover, no pegcetacoplan-related ocular effects occurred during the toxicity study, and there were no microscopic findings in the eye at termination.

Target organs were blood, lung, spleen, liver, kidney and SC dose site. At the end of the study, radioactivity was still quantifiable in 19 tissues against 25 tissues at the beginning. At all timepoints, the radioactivity in blood was higher than in all tissues measured. Regarding excretion, the mean urinary recovery of radioactive dose through 504 hours (3 weeks) post-dose was 44.55%.

The distribution in Placenta was evaluated in pregnant female *Cynomolgus* monkeys, after a once daily SC administration of 28mg/kg/day of pegcetacoplan during the period of organogenesis through the second trimester of pregnancy (approximately 120 doses). Pegcetacoplan has been found in foetus and the mean concentration was 2.50µg/mL, representing a low level of placenta transfer (<1% of mean maternal concentration 1770 µg/mL) at the given dose.

Metabolism

Metabolism of Pegcetacoplan has not been specifically studied but it expected to be catabolized like PEGylated peptide/protein conjugates. In a study in monkeys, Pegcetacoplan was cleared slowly from the circulation (with mean serum concentration of 50 and 20% at 1 and 2 weeks after 2 consecutive days at 84mg/kg IV injection).

Excretion

The mean urinary recovery of radioactive dose through 3 weeks post dose was 44.55% in Monkey after dose of 7mg/kg SC. The excretion in milk was evaluated in the monkey study, the pegcetacoplan concentration in milk samples decreased with time but remained quantifiable until Post-Partum day 14 and 28 at doses of 7 and 28 mg/kg/day. On PPD 14, the concentration ranged from 29 to 287 ng/mL at 7 mg/kg/day and ranged from 42 to 272ng/ml at 25 mg/kg/day. The ratio concentration serum: milk on PPD14 demonstrate a low level of excretion in milk (<1%). Finally, pegcetacoplan has not been quantified in the offspring, demonstrating a minimal risk of exposure in case of breast finding or pregnancy.

Pharmacokinetic drug interaction

The drug drug interaction was evaluated in three *in vitro* metabolism assays, two studies assessing the inductor or inhibitor potential of pegcetacoplan and one study assessing if Pegcetacoplan serve as substrate and/or inhibitor for human drug transporters (Study 17COTX-002). Pegcetacoplan showed no apparent induction or inhibition of cytochrome P450 in human hepatocytes or liver microsomes at any concentrations tested (between 0.1 and 6mg/kg). These two studies suggest low potential to induce or inhibit the metabolism of drugs which are substrates of these cytochromes P450s. The assay evaluating human drug transporter interaction with pegcetacoplan as a substrate and/or inhibitor for key solute carrier (SLC) transporters and key ATP-binding cassette (ABC) transporters showed that pegcetacoplan was not a substrate nor an inhibitor of transporters at any concentrations tested (between 0.06 and 0.6 mg/kg).

These studies demonstrate that pegcetacoplan has a low risk to interact with other drugs.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No single-dose toxicity studies were conducted specifically with pegcetacoplan. The data used for single dose toxicity were obtained from the definitive 28-day studies in rabbit and monkeys at 140mg/kg in SC injection, from the pharmacology study in monkeys at 84mg/kg in IV injection on day 1 and 2, and from safety pharmacology in monkeys at 140mg/kg SC injection. These results showed a good tolerance of pegcetacoplan in different species (monkeys and rabbits) up to 140mg/kg in IV or

SC injection and no adverse effect on cardiovascular or respiratory function were noted. Also, the genotoxic study 13BTX-003 in mice showed a good tolerance following two consecutive daily 2000mg/kg IV doses. Pharmacological studies showed that pegcetacoplan was not pharmacologically active in non-primate species. The binding of pegcetacoplan on C3 is species-dependent. The peptidic domains to bind to human C3 is not conserved in non-primate species. The pharmacological activity in primates was demonstrated in *in vitro* and *in vivo* assays. However, to support the marketing authorization a second nonclinical toxicology species was considered necessary thus the rabbit was chosen because this species was presented tissue vacuolation associated with the PEG moiety and the renal tubular degeneration and it has been used also as a model to assess local irritancy and tolerability.

2.5.4.2. Repeat dose toxicity

The first pilot, non-GLP compliance studies were conducted in rabbits and monkeys during 7 days to determine the toxicological potential and the toxicokinetic of APL-2 (Pegcetacoplan) at 20mg/kg/day or PEG40 at 16mg/kg/day. After repeated injections each day, no clinical signs, injection signs reactions or changes in body weight or clinical pathology parameters were observed. Also, no macro or microscopic findings associated. Regarding toxicokinetic, serum pegcetacoplan concentration and T1/2 increased each day with dose, suggesting an accumulation of product. In Rabbit, no sex difference was observed and no production of ADA against pegcetacoplan or PEG 40 were observed in monkeys.

During the 28-day GPL compliance definitive studies in rabbits and monkeys, pegcetacoplan was administered at 7, 28 and 140mg/kg/day and 2 control groups were added: group PEG40 at 112mg/kg and group diluent alone (Dextrose 5%). A period of recovery of 28 days (after injections of 140mg/kg) was performed after the 28-day study to evaluate the reversibility of effects.

From the rabbit study, some microscopic findings were observed in all groups, such as infiltrates of macrophages (histiocytes) or resident macrophages with abundant vacuolated cytoplasm and vacuolation of epithelial cells in the choroid plexus, kidney and synovium. The issue of the vacuoles in the choroid plexus of the brain has already been raised and discussed, especially for paediatric population (see CHMP Safety Working Party's response to the PDCO regarding the use of PEGylated drug products in the paediatric population: https://www.ema.europa.eu/en/chmp-safety-working-partys-response-paediatric-committee-regarding-use-pegylated-drug-products).

At 28mg/kg, hematologic effects were observed: increase of red cells and reticulocytes counts and a decrease of platelet and leucocytes counts and serum glucose and potassium concentrations. Only reticulocytes count return to or towards diluent control values after 28 day dose free recovery period. Concerning the reversibility of leucocyte count, a contradiction has been noted: In the summary document, the hematologic effects (cited above) have been not considered reversible (except the reticulocytes), but in the study report 13CATX-003 (p.29) the white blood cell count (leucocyte) return to the diluent control levels following a 28 day dose free recovery period. Concerning this discrepancy, the applicant amended the summary document with the correct fact: the reticulocyte and leucocytes counts returned to or toward diluent control values after 28-day dose free recovery period. Also, some effects on spleen and on injection sites have been observed: an increase number of vacuolated macrophages in red pulp in spleen and at 140 mg/kg an increase of severity inflammatory cell infiltrates. These effects were more important at 140mg/kg and persisted through the 28 days of recovery. It should be noted that the reversibility is known only for the group receiving 140mg/kg, and not for the group receiving 28mg/kg as mentioned by the Applicant.

The microscopic findings, such as infiltrates of macrophages and vacuolation of epithelial cells, were also observed in PEG40 group, indicating the imputability of PEG40. A slight increase in incidence

and/or severity at 140mg/kg suggests an additional effect of pegcetacoplan. Also, at 140mg/kg a minimal kidney degeneration was observed in one female after terminal sacrifice and on male after recovery period. Consequently, the NOAEL was considered to be 28mg/kg.

From the monkeys study (13CATX-0004), at 28mg/kg/day, microscopic vacuolation and minimal degeneration in kidney were observed and not considered as reversible, but as previously mentioned, the reversibility is not determined at 28mg/kg. No explanation has been provided concerning the reversibility of the tubular degeneration in kidney in Rabbits and Monkeys, nor the subsequent clinical relevance. At 140mg/kg, changes on coagulation parameters such as a decrease of 42% of fibrinogen was observed, but this finding was reversible after 28 day recovery. At 140mg/kg and also in PEG40 group (but less severe), the non-reversible effects after recovery period, were subcutaneous inflammatory cells infiltrates at the injection's sites. As in the rabbit group, microscopic findings (infiltrates of macrophages, epithelial vacuolation) were observed in control group PEG40, and can be attributed to the PEG40. The NOAEL was considered to be 7mg/kg. The on and off targets effects was described in the dossier. The main effects were off target effect (related to PEG) and they were observed in rabbit and monkeys, excepted hematological toxicities but this change is not totally understood.

In the study 14CATX-004, the applicant compared a Pegcetacoplan produced by a different manufacturer in monkeys. At the dose of 28mg/kg and PEG40 at 25.6mg/kg, the effects observed were minimal to mild epithelial vacuolation in the choroid plexus, microscopic findings in the kidney. These results showed that the pegcetacoplan manufactured by that manufacturer is comparable to those with pegcetacoplan at 28mg/kg/day in the previous 28-day definitive study.

Another study (19CATX-003) was conducted in monkeys to qualify toxicologically some components that form in pegcetacoplan after accelerated degradation at 40°C for 7 days. Three monkeys/sex/groups received either heat- degraded pegcetacoplan (28 mg/kg/day), non-degraded pegcetacoplan (28 mg/kg/day) or vehicle (acetate-buffered 4.1% sorbitol) alone. Non degraded or heat depredated Pegcetacoplan were well tolerated. The effects observed (minimal tubular degradation in the kidney and microscopic findings at the injections sites) were similar with the previous 28-day study. The vehicle tested in group 3 is different from the vehicle used in toxicological study. The applicant provided an explanation concerning the different formulations used during the Pegcetacoplan development.

In the 6 months study in rabbit, the doses tested were 1, 7 and 28 mg/kg and two additional groups were added with control PEG40 26mg/kg and diluent alone (5% dextrose). Of note, PEG40 was less concentrate in 6 and 9 months study than 28-day study. In 28mg/kg and PEG40 groups, some changes in haematology parameters were observed (minimally reduced red blood cell counts, hematocrit and haemoglobin in female), but these effects were attributable to PEG40. Similarly, to 28-day definitive study (13CATX 003), effects related to PEG40 are observed (infiltrates of macrophage, epithelial vacuolation). The severity and incidence were comparable between 28 mg/kg group and PEG40 group. These changes were also observed at 1 and 7 mg/kg with a severity and incidence dose dependent, reflective of increase levels of PEG40. Also, in the kidney, microscopic findings were observed (minimal tubular degeneration) at all doses of pegcetacoplan as well as in PEG40 group and diluent group.

In general, during 9 months pegcetacoplan was well tolerated in Monkeys. However, in the 7 and 28mg/kg groups, hematologic parameters have been modified (reductions in mean red cells mass of 10 and 15% respectively compared to baseline). In all groups treated by pegcetacoplan, some microscopic findings PEG-40 related such as infiltrates of macrophages, epithelial vacuolation and minimal tubular degeneration in kidney have been observed at 3 months (interim sacrifice) and 9 months in the PEG40 groups. The NOAEL was 7mg/kg. The vacuoles observed in non-clinical studies

were not reversible even after a recovery period of 28-days. The Applicant elected not to include recovery groups on the chronic studies based on the not important severity of effects and the reversibility expected. The reversibility of vacuolation depends of the kind of PEG, the size and the mode and duration of administration. For pegcetacoplan, the only recovery study has shown that the effects were not reversible.

Moreover, the description of degeneration/regeneration in the study report was not clear. Also, the microscopic studies of vacuole were present in order to confirm the non-severity of effect.

Different routes of administration were compared in rabbits and monkeys: intravenous versus subcutaneous (future marketed form). For both species and for both routes of administration the effects have been similar. From 1mg/kg in SC and in IV, vacuolation in epithelial cell in kidney in rabbits and in mesenteric lymph in monkeys was observed in one male.

The toxicokinetic parameters from all studies showed an increase of AUC 0-24h with repeat dose between day 1 and day 28 suggesting an accumulation of pegcetacoplan but from 6 and 9 months studies, a steady state was reached on day 28 (no difference in exposure on day 91, 180 and 273) suggesting a saturation. The mean AUC increase was dose proportional for 1 or 7 and 28mg/kg and from day 1 to day 28, but from day 28 and from 28mg/kg, the AUC increased in a generally less than dose proportional manner for the 20-fold increase for doses from 7 to 140 mg/kg/day, as exposure increased by approximately 12-fold on Day 1 and by approximately 4.7-fold on Day 28. There was no gender differences in pegcetacoplan exposure. In the rabbit 28-day study, Anti-Drug antibodies (ADA) were detected in all pegcetacoplan groups without any effects. In the 9 months Monkey study, ADA were confirmed in 5 samples at 1mg/kg/day on day 14, day 91 and day 273 while no ADA were detected in 28-day study. The animal exposure seems sufficient during the long studies (6 and 9 months), especially since the administration was daily while it will be bi-weekly in human.

This interspecies comparison focussed on PEG concentration. PEG exposure was dose proportional to pegcetacoplan dose. At the highest dose, animals were 30 times more exposed than humans.

2.5.4.3. Genotoxicity

The genotoxic GLP-compliance studies were conducted on separate bacterial mutation (Ames) on several lots, on *in vitro* mammalian cell with or without metabolic activation system S9 (micronucleus test) and on mice (Micronucleus test *in vivo*) by injection IV as two consecutive daily doses of up to 2000mg/kg. Several strains of salmonella Typhirium and Escherichia coli strain were tested covering different possible effects. As expected with peptide, the results for all tests were negative. In conclusion the potential genotoxic of pegcetacoplan is negative, based on these results.

2.5.4.4. Carcinogenicity

Rodent carcinogenicity bioassays on pegcetacoplan have not been conducted. Since pegcetacoplan is pharmacologically active only in humans and non-human primates, such studies would not add scientific value. The uniformly negative results of the genotoxicity assays indicate that pegcetacoplan is not mutagenic or clastogenic. There is no evidence from the toxicity studies that pegcetacoplan is either an endocrine disrupter, cell-cycle disregulator or a pro-inflammatory agent. Regarding the pharmacologic action of pegcetacoplan, whereas it has traditionally been viewed that complete-cascade inhibition may potentially be tumor-promotional through decreased immunosurveillance, the weight of more recent evidence suggests the converse to be true, i.e. that complement activation enhances tumor growth and increases tumor metastasis (Afshar-Kharghan, 2017). Indeed, complement inhibition has been postulated as a potential oncology therapy (Zhang et al., 2019).

2.5.4.5. Reproductive and developmental toxicity

Pegcetacoplan was demonstrated to be pharmacologically active in *Cynomolgus* monkeys but did not elicit a pharmacological response in rats and rabbits (study 19CFPH-001). Therefore, the reason for conducting embryo-foetal development studies (even no pivotal) in non-pharmacologically-relevant rat and rabbit species is unclear, and also questionable from a 3R's perspective. In that case, a single enhanced pre- and post-natal development (ePPND) study is acceptable.

The potential for effects on fertility could be assessed by evaluation of reproductive tract in repeat-dose toxicity studies of at least 3 months duration using sexually mature monkeys at study initiation. The latter criterion was likely not fulfilled in study 15CATX-004 since monkeys were 2-4 years old at treatment initiation. The applicant acknowledges the concern and reports some difficulties to obtain monkeys aged 4-5 years which would be fully mature; the oldest available monkeys were used at the time of the study conduct. In this context, a detailed evaluation of the state of sexual maturity of *Cynomolgus* monkeys used in the pivotal 9-month toxicity study was performed. In males, 2-3 animals per group were found to be in the early adult/ adult age at the time of terminal examination based on testis weight and histopathology. In females, it is relied on publications defining the age of sexual maturity in monkeys according to the age of first menarche: 24-30 months (Buse et al 2008) or 1195 days (~40 months: Kobayashi et al, 2018), keeping in mind that full maturity is not reached at this age. All animals were older than 24 months of age at initiation of treatment, and 2-4 animals per group reached the first menarche criterion of 1195 days at least 30 days before the end of the dosing period. Sexual development would have been active for the majority of these monkeys during the latter part of the study. In addition, there is no indication in the published literature for a potential adverse effect on fertility driven by the pharmacological activity of pegcetacoplan.

No treatment-related effect was observed in (non GLP-compliant) embryo-foetal development studies conducted in rats and rabbits. The clinical relevance of these results is unclear since they were obtained in pharmacologically irrelevant species. In addition, the design of these studies was limited due to their nonpivotal nature (e.g. low number of litters, no visceral/skeletal foetal examinations…).

In a pilot study conducted in *Cynomolgus* monkeys, no adverse developmental treatment-related outcome was observed following treatment from GD20 to GD140 at the dose of 28 mg/kg/day (x2.6-fold patient exposure at the MHRD based on either Cmax or AUC). Epithelial and macrophage vacuolation was reported in the choroid plexus of the brain of treated females, but such findings were not observed in foetal brains. Toxicokinetic data suggest limited foetal exposure to pegcetacoplan since concentrations measured in the umbilicus were 0.15% those measured in maternal serum.

Increased incidence of abortions and stillbirth resulting in an increase in total combined foetal loss (above historical control range) were observed in the high dose group treated at 28 mg/kg/day. There was no observed treatment-related teratogenic effect, and no effect on the development at 7 mg/kg/day and in the remaining offspring at 28 mg/kg/day.

Animal-to-human exposure ratios reached 1.3 at the NOAEL of 7 mg/kg/day, and 2.9 at the dose of 28 mg/kg/day. These figures were calculated based on GD111 data. Data reported at GD140 were extrapolated from only one time-point (8 hours post-dose), and the TK data obtained in the pilot embryofoetal study showing comparable exposure levels in dams on GD111 and GD140 (at 28 mg/kg/day). The pilot study suggested low foetal exposure to pegcetacoplan based on a low foetal umbilicus/maternal serum ratio (0.15%). In the ePPND study, a time-related decrease in systemic exposure was reported in maternal animals with quantifiable levels up to PND14 (7 mg/kg/day) or 28 (28 mg/kg/day). Serum concentrations could not be quantified in infants from day 14 of age, with also low milk/serum ratios at this occasion (no greater than 0.52%).

Excessive activation or inadequate regulation of the complement system lead to placental dysfunction. Regal *et al* (2015) report that complement regulation is apparent at the placental interface from early pregnancy with some degree of complement activation occurring normally throughout gestation. In the present study, no treatment-related effect was reported at examination of (available) placentae. The applicant also relies on this publication to indicate that the increase in abortions and stillbirths seen in the ePPND study was not expected because regulation of the complement cascade is beneficial to pregnancy maintenance. Although it cannot be excluded that the pharmacological regulation of the complement system may trigger different effects in healthy vs. diseased pregnant animals, there is currently no sufficient rationale to consider that the adverse foetal outcome in the ePPND study are not clinically relevant.

Toxicology studies in juvenile animals have not been conducted. In the pivotal 9-month repeat-dose toxicity study in *Cynomolgus* monkeys, animals ranged from approximately 2 years (i.e., adolescent) to approximately 4 years (i.e., young adult) of age at the time of study initiation, thus, providing a representative view of potential effects of pegcetacoplan on postnatal growth and development in the intended paediatric population. As the agreed paediatric investigation plan for pegcetacoplan in the treatment of PNH (P/0149/2020) includes adolescents between the ages of 12 and <18, but not younger children or infants, data from the existing nonclinical study package is considered to sufficiently capture potential adverse effects on organ systems undergoing postnatal development during this range of time.

2.5.4.6. Toxicokinetic data

Species	Study Number	Study Duration	Dose (mg/kg/day)	C_{max}[a] (µg/mL)	$AUC_{0\text{-}24_0}$ (µg.h/mL)	Ratio of animal to human exposure[c]	
						C_{max} (µg/mL)	$AUC_{0\text{-}24}$ (µg.h/mL)
Rabbit	15CATX-003	6 months	1	45	993	0.06	0.06
			7	310	6980	0.46	0.45
			28	934	21500	1.39	1.39
	13CATX-003	1 month	140[d]	2890	66250	4.31	4.27
Monkey	15CATX-004	9 months	1	179	4035	0.27	0.26
			7	**970**	**21950**	**1.45**	**1.42**
			28	2000	45150	2.98	2.91
	13CATX-004	1 month	140[d]	4175	94400	6.22	6.09
	18CATX-001	4 months[e] (Pre-postnatal)	**7**	**896**	**20500**	**1.34**	**1.32**
			28	1930	44300	2.88	2.86
Human	APL2-302	A maximum of approximately 72 weeks	1080 mg twice weekly	671[f]	15506[g]		

2.5.4.7. Local Tolerance

No specific study for local tolerance has been conducted. The local tolerance has been assessed according to the effects observed in repeated dose studies. No injection-site reactions were noted but a slight increase of inflammatory cells or an accumulation of vacuolated macrophages was observed at doses ≥28 mg/kg/day in rabbits and monkeys. The presence of vacuolated macrophages is expected and known with repeated injections of PEG40.

2.5.4.8. Other toxicity studies

Antigenicity

No specific antigenicity study has been conducted. The results obtained from toxicological studies and toxicokinetic showed a low antigenicity at titers of 1:20 to 1:500 and pegcetacoplan is less antigenic when the administration is performed by IV route (titers of 1:20 to 1:100). As the efficacy is not impacted, the ADA do not seem neutralizing. ADA are directed against PEG40 and are dependent on PEG ramification.

Immunotoxicity

No specific immunotoxicity study has been conducted. In this case, the non-clinical study conducted in rabbits showed some modifications of hematology parameters such as a decrease of leucocytes count, and a production of antibodies (ADA) against Peg40 in rabbit and more weakly in monkeys. As the efficacy is not impacted, the ADA do not seem neutralizing and appear late. ADA are directed against PEG40 and are dependent on PEG ramification. However, no increased incidence of infections has been noted in rabbit or monkeys. In monkeys no changes in clinical pathology parameters (serum protein concentration or total protein or leucocytes count) has been observed while a decrease of leucocytes count has been observed in rabbit. Pegcetacoplan is weakly to moderately antigenic to rabbits and minimally to monkeys by the ADA production.

2.5.5. Ecotoxicity/environmental risk assessment

Persistance Bioaccumulation and Toxicity screening resulted in logKow values lower than 4.5, so pegcetacoplan is hydrophile and no bioaccumulable in the environment. Even if based on the results of biodegradability test, pegcetacoplan cannot be characterised as readily biodegradable and that a test protocol OECD 308 on sediment system should be required (in accordance with EMEA/CHMP/SWP/4447/00 guideline (EMEA, 2006) and the Questions and Answers on the Guideline CHMP/SWP/44609/2010 (EMA, 2011a)), the environmental release of PEG from pegcetacoplan will be negligible in comparison to the release from other consumer products (cosmetics and body care products). Furthermore, a full ECHA registration dossier is available for PEG[1]. This latter demonstrates that additional degradability testing for the PEG-moiety in pegcetacoplan is unnecessary and therefore not warranted.

PECsurface water calculated is 3.021 ng/L, which is below the action limit. A Phase II assessment is deemed not necessary. Usually the Fpen used is 1%, in this case, the applicant chose to evaluate the PECWS with a lower Fpen of 0.00159% in view of the rarity of the PNH. Although the reliability of data is weak, it is considered very unlikely that the Fpen reaches values that could increase the PEC above the ERA action limit. Thus, the Fpen used to evaluate the PECws is acceptable.

2.5.6. Discussion on non-clinical aspects

The non-clinical development program for pegcetacoplan was designed in accordance with ICH M3 guidelines.

The pharmacological profile of pegcetacoplan was demonstrated in *in vitro* assays and *in vivo* in *Cynomolgus* monkey. Pegcetacoplan inhibits the alternative and classical pathways of complement system by binding to C3 and C3b with affinity of 15nM and 21,3 nM respectively. The secondary or off target pharmacology has not been specifically investigated considering that the peptidic domains of the molecule are a derivative of Compstatin and the PEG moiety is known to be biologically inert. However,

[1] https://echa.europa.eu/registration-dossier/-/registered-dossier/11848/

these justifications were not considered acceptable. The assays on canal hERG to assess cardiac function was conducted specifically. Up to 300µM, there was little to no reduction in hERG current amplitude without or with Human Serum Albumin. Several endpoints such as cardiac and respiratory functions from the toxicological studies were evaluated for safety pharmacology. According to ICH M3 guidelines, several endpoints such as the tidal volume, respiratory rate or hemoglobin oxygen saturation should be measured from the toxicological studies. In study 13CATX-005, the respiratory volume and the tidal volume were assessed. However, concerning the potential action on Central Nervous System, Pegcetacoplan distribution in brain was quantified in primates (Study 17MTX00001) with value below the limit of quantification. Moreover, pegcetacoplan does not cross the blood brain barrier and clinical observation did not suggest any behaviour trouble related to impairment of CNS.

No pharmacodynamic drug interactions study has been conducted to date. Data obtained from the pharmacokinetic study did not suggest a major interaction between cytochrome P450 enzyme or drug transporter and pegcetacoplan. However, it should be noted that pegcetacoplan will be co-administrated with eculizumab to avoid the risk of hemolysis. The AH50 values of subjects from Studies CP0514 and APL2-302 increased toward normal, reflecting a persistent, partial, inhibition of the alternative pathway of complement pathway with repeated SC dosing of pegcetacoplan. The interaction between pegcetacoplan and eculizumab, a C5 inhibitor, was evaluated as part of the PopPK analysis when co-administered to PNH subjects (studies APL2-302 and CP0514). It is expected that pharmacodynamic interactions between C3 and C5 inhibitors are very unlikely since both inhibit different parts of the complement cascade, thus the lack of pharmacodynamics drug interaction study is acceptable.

According to the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**), the information related to analytical methods is acceptable. Absorption, distribution, metabolism and excretion of pegcetacoplan have been thoroughly evaluated following intravenous and subcutaneous administration (single and repeated) in *Cynomolgus* monkeys, species used for pharmacology and toxicology studies. No plasma protein binding studies were performed with pegcetacoplan which is acceptable. The distribution in Placenta was evaluated in pregnant female *Cynomolgus* monkeys and Pegcetacoplan has been found in foetus and the mean concentration was 2.50µg/mL, representing a low level of placenta transfer (<1% of mean maternal concentration 1770 µg/mL) at the given dose.

The toxicological profile of pegcetacoplan has been evaluated during repeat-dose toxicity studies in *Cynomolgus* monkeys and rabbit. No Single-dose toxicity studies were conducted specifically with pegcetacoplan. The data used for single dose toxicity were obtained from the definitive 28-day studies in rabbit (Study 13CATX-003) and monkeys (Study 13CATX-004) at 140mg/kg in SC injection, from the pharmacology study 16CATX-0003 in monkeys at 84mg/kg in IV injection on day 1 and 2, and from safety pharmacology in monkeys (13CATX-0005) at 140mg/kg SC injection. These results shown a good tolerance of pegcetacoplan in different species (monkeys and rabbits) up to 140mg/kg in IV or SC injection and no adverse effect on cardiovascular or respiratory function were noted. In pharmacological studies, it was shown that pegcetacoplan was pharmacologically active only in non human primate species. After 7 days of pegcetacoplan at 20mg/kg in rabbit and monkeys no macro or microscopic findings were observed.

From the 28-day rabbit study (13CATX-0003), some microscopic findings were observed in all groups, such as infiltrates of macrophages (histiocytes) or resident macrophages with abundant vacuolated cytoplasm and vacuolation of epithelial cells in the choroid plexus, kidney and synovium. The problem of the vacuoles in the choroid plexus of the brain has already been raised and discussed, especially for paediatric population (CHMP Safety Working Party's response to the PDCO regarding the use of PEGylated drug products in the paediatric population).

Hematologic effects were observed: increase of red cells and reticulocytes counts and a decrease of platelet and leucocytes counts and serum glucose and potassium concentrations. Only reticulocytes counts return to or towards diluent control values after 28 day dose free recovery period.

From the monkeys' study, at 28mg/kg/day, microscopic vacuolation and minimal degeneration in kidney were observed and not considered as reversible, but as previously mentioned, the reversibility is not determined at 28mg/kg. No explanation has been provided concerning the reversibility of the tubular degeneration in kidney in Rabbits and Monkeys, nor the subsequent clinical relevance.

Another study (19CATX-003) was conducted in monkeys to qualify toxicologically some components that form in pegcetacoplan after accelerated degradation at 40°C for 7 days. The effects observed (minimal tubular degradation in the kidney and microscopic findings at the injections sites) were similar with the previous 28-day study.

During the 6 months rabbit study, some changes in haematology parameters were observed (minimally reduced red blood cell counts, haematocrit and haemoglobin in female), but this effects were attributable to PEG40. In general, during the 9 months study in Monkeys, pegcetacoplan was well tolerated with some hematologic parameters' changes. Concerning the lack of data on PEG vacuole reversibility of 6 and 9 months and the absence of reversibility, according to ICH M3 guideline, the applicant demonstrated that reversibility was not evident within 28 days of dosing cessation, and the literature suggested that prolonged durations may be needed to show reversibility complete or at least partial in some tissues or organs. Moreover, the immunochemistry data were not provided (not conducted). However, the vacuolation were described in literature (Rudmann et al, 2013) and comparable to pegcetacoplan. The clinical relevance is unknown and the reversibility was not evaluated from 6 and 9-months studies. This justification is acceptable with regards to the indication and the adult population. As regard the non-clinical data, section 5.3 of the SmPC states that "Repeat dose studies were conducted in rabbits and *Cynomolgus* monkeys with daily subcutaneous doses of pegcetacoplan up to 7 times the human dose (1 080 mg twice weekly). Histologic findings in both species included dose dependent epithelial vacuolation and infiltrates of vacuolated macrophages in multiple tissues. These findings have been associated with large cumulative doses of long chain PEG in other marketed PEGylated drugs, were without clinical consequence, and were not considered adverse. Reversibility was not demonstrated in the pegcetacoplan animal studies after one month and was not evaluated for a longer duration. Data from literature suggest reversibility of PEG vacuoles. Renal tubular degeneration was observed microscopically in both species at exposures (Cmax and AUC) less than or comparable to those for the human dose and was minimal and nonprogressive between 4 weeks and 9 months of daily administration of pegcetacoplan. Although no overt signs of renal dysfunction were observed in animals, the clinical significance and functional consequence of these findings are unknown.

The genotoxic GLP-compliance studies, were conducted on separate bacterial mutation (Ames) on several lots, on *in vitro* mammalian cell with or without metabolic activation system S9 (micronucleus test) and on mice (Micronucleus test *in vivo*) according to ICH M3 Guidelines. As expected with a peptide, the results for all tests were negative. In conclusion the potential genotoxic of pegcetacoplan is negative, based on these results.

Rodent carcinogenicity bioassays on pegcetacoplan have not been conducted. Since pegcetacoplan is pharmacologically active only in humans and non-human primates, such studies would not add scientific value. The uniformly negative results of the genotoxicity assays indicate that pegcetacoplan is not mutagenic or clastogenic. This is considered acceptable.

Reproductive and developmental toxicity

Pegcetacoplan was demonstrated to be pharmacologically active in *Cynomolgus* monkeys only. It did not elicit a pharmacological response in rats and rabbits, therefore, the reason for conducting embryo-foetal development studies (even nonpivotal) in these species is unclear and debatable. Considering also the limitations of these studies due to their nonpivotal nature (e.g. low number of litters, no visceral/skeletal foetal examinations…), they were not considered for a human risk assessment.

The following statement is provided in section 5.3 of the SmPC: "Pegcetacoplan treatment of pregnant cynomolgus monkeys at a subcutaneous dose of 28 mg/kg/day (2.9 times the human steady state Cmax) from the gestation period through parturition resulted in a statistically significant increase in abortions or stillbirths. No maternal toxicity or teratogenic effects were observed in offspring delivered at term. Additionally, no developmental effects were observed in infants up to 6 months postpartum. Systemic exposure to pegcetacoplan was detected in foetuses from monkeys treated with 28 mg/kg/day from the period of organogenesis through the second trimester, but the exposure was minimal (less than 1%, not pharmacologically significant)."

No fertility study was conducted with pegcetacoplan. The applicant relies on the repeat-dose toxicity studies in monkeys showing no adverse effects of pegcetacoplan in males or females sex organs. This strategy is in accordance with current recommendations for biopharmaceuticals demonstrated to be pharmacologically relevant only in non-human primates. However, only results of studies of at least 3 months duration initiated in sexually mature animals should be considered in that case. This criterion was likely not fulfilled in the 9-month monkey study (no.15CATX-004) since animals were 2-4 years old at treatment initiation. The applicant acknowledges the concern and reports some difficulties to obtain monkeys aged 4-5 years which would be fully mature; the oldest available monkeys were used at the time of the study conduct. In this context, a detailed evaluation of the state of sexual maturity of *Cynomolgus* monkeys used in the pivotal 9-month toxicity study was performed. In males, 2-3 animals per group were found to be in the early adult/ adult age at the time of terminal examination based on testis weight and histopathology. In females, it is relied on publications defining the age of sexual maturity in monkeys according to the age of first menarche: 24-30 months (Buse et al 2008) or 1195 days (~40 months: Kobayashi et al, 2018), keeping in mind that full maturity is not reached at this age. All animals were older than 24 months of age at initiation of treatment, and 2-4 animals per group reached the first menarche criterion of 1195 days at least 30 days before the end of the dosing period. Overall, the applicant's conclusion that sexual development would have been active for the majority of these monkeys during the latter part of the study is agreed. In addition, it is explained that there is no indication in the published literature for a potential adverse effect on fertility driven by the pharmacological activity of pegcetacoplan. Therefore, the following statement is provided in section 4.6 of the SmPC/ Fertility "No animal or human data on the effect of pegcetacoplan on fertility are available. In toxicity studies, there were no microscopic abnormalities in male or female reproductive organs in monkeys (see section 5.3). Data from studies conducted in pharmacologically-irrelevant species (rabbit) have not be reflected in the SmPC.

In an enhanced pre- and post-natal development toxicity study performed in monkeys, maternal animals were treated s.c. at 0, 7, and 28 mg/kg/day from GD20 to parturition, and then monitored with their offspring up to 6 months postnatal. At the top dose (x2.9-fold clinical exposure) increases in abortions and stillbirth resulting in an increase in total combined foetal loss (above historical control range) were observed. In infants, no treatment-related effect was reported at external, visceral, and skeletal examinations, morphometric measurements, neurobehavioral or neurological evaluations, TDAR assessments, gross pathology and histopathology (including brains), organ weights, or heart morphology evaluations. The maternal and developmental NOAEL was 7 mg/kg/day, corresponding to exposure levels at GD 111 similar (x1.3) to those reached in patients at the recommended dose. During the postnatal period, systemic exposure levels in maternal animals declined up to postnatal day 14/28 whereas pegcetacoplan could not be quantified in infants from postnatal day 14 to 182.

Pegcetacoplan was excreted in maternal milk, albeit minimally (milk/serum ratios on postnatal day 14 of maximum 0.52%). In a pilot embryofoetal monkey toxicity study, the foetal umbilicus/maternal serum ratio of 0.15% measured at C-section on GD 140 also suggested low foetal exposure to pegcetacoplan. These results were reported adequately in section 5.3 of the SmPC.

No specific study for local tolerance has been conducted. The local tolerance has been assessed according to the effects observed in repeated dose studies. No injection-site reactions were noted but a slight increase of inflammatory cells or an accumulation of vacuolated macrophages were observed at doses ≥28 mg/kg/day in rabbits and monkeys.

No specific studies of antigenicity, immunotoxicity have been conducted. This is considered acceptable for this product.

Persistance Bioaccumulation and Toxicity screening resulted in logKow values lower than 4.5, so pegcetacoplan is hydrophile and no bioaccumulable in the environment. Even if based on the results of biodegradability test, pegcetacoplan can not be characterised as readily biodegradable and that a test protocol OECD 308 on sediment system should be required (in accordance with EMEA/CHMP/SWP/4447/00 guideline (EMEA, 2006) and the Questions and Answers on the Guideline CHMP/SWP/44609/2010 (EMA, 2011a)), the environmental release of PEG from pegcetacoplan will be negligible in comparison to the release from other consumer products (cosmetics and body care products). Furthermore, a full ECHA registration dossier is available for PEG. This latter demonstrates that additional degradability testing for the PEG-moiety in pegcetacoplan is unnecessary and therefore not warranted. PECsurface water calculated is 3.021 ng/L, which is below the action limit. A Phase II assessment is deemed not necessary.

2.5.7. Conclusion on the non-clinical aspects

Overall, the non-clinical package available for pegcetacoplan is considered sufficient to support the marketing authorisation for the proposed indication.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- **Tabular overview of clinical studies**

Ten clinical studies were submitted evaluating PK, PD and PK/PD relationship:

- 5 studies in healthy volunteers (CP1014, CP0713-1, 101, 102, 401)
- 1 study in subjects with renal impairment (205)
- 4 studies in patients with PNH (APL2-302, 204, 202, CP0514)

Full PK sampling was performed in studies with healthy volunteers and subjects with renal impairment, while studies with PNH patients employed trough sampling only.

Various formulations and dosing regimens were investigated during the clinical development. The intended therapeutic dosing regimen for patients with PNH is 1080 mg pegcetacoplan (10 mM acetate-

buffered formulation containing 4.1% sorbitol) administered by SC infusion twice weekly, also studied in the pivotal Phase 3 study (APL2-302).

Table 2: Overview of clinical studies providing PK data for pegcetacoplan

Study identifier	Phase	Description	Dose	Formulation	n	Subjects
CP0713-1	1	SAD	45-1440 mg	5% w/v dextrose, no buffer	31	Healthy subjects
CP1014	1	MAD	30-270 mg QD for 28 days	5% w/v dextrose, no buffer	20	Healthy subjects
101	1	PK, safety, tolerability	360 mg QD 1300 mg twice weekly 2600 mg once weekly **1080 mg twice weekly**	10 mM acetate buffer, pH 5.0, approximately 4% sorbitol	40	Healthy subjects
102	1	Japan bridging	180-1440 mg	Lyophilized drug substance (to be reconstituted in 5% w/v dextrose)	20	Healthy Japanese subjects
401	1	SAD IV	200-2300 mg	10 mM acetate buffer, pH 5.0, 0.9% NaCl	20	Healthy subjects
205	1	Renal impairment	270 mg	Lyophilized drug substance (to be reconstituted in 5% w/v dextrose)	16	Subjects with severe RI
CP0514	1b	Single and MAD, add-on to eculizumab	25-50 mg 5-360 mg QD		9	PNH patients
202	2a	MAD w/o eculizumab	270-360 mg QD		4	PNH patients
204	1b	MAD w/o eculizumab	180-360 mg QD		22	PNH patients
302	3	Efficacy, safety	**1080 mg twice weekly**	10 mM acetate buffer, pH 5.0, approximately 4% sorbitol	41	PNH patients

Additionally, 3 *in vitro* studies were conducted with human biomaterial to evaluate drug interactions.

Population PK analysis and exposure-response analysis were performed.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Methods

Bioanalytical methods were used for determining serum pegcetacoplan concentration, for monitoring immunogenicity and for the measurement of pharmacodynamics parameters.

Serum pegcetacoplan concentration

Concentrations of pegcetacoplan (APL2) were determined in human serum using the liquid chromatography tandem mass spectrometry (LC-MS/MS) method. Bioanalytical methods were satisfactorily validated in accordance with the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1). LC-MS/MS methods were developed and validated at three different laboratoriesand were used for bioanalysis of the samples across studies.

Immunogenicity

- *ADA assay*

In early clinical studies (CP0713, CP1014, 401, CP0514 and 6 subjects from Study 204), ELISA-based ADA assay was used to detect antibodies against pegcetacoplan in human serum. In later clinical studies, a standard multi-tiered approach was employed including screening, confirmatory and titer assays to evaluate anti-drug antibodies in accordance with EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1). In those studies, ECL-based ADA assay was used to detect antibodies against peptide moiety of pegcetacoplan in parallel with ELISA-based ADA assay to detect antibodies against PEG moiety of the drug molecule. Assays were developed at two different sites.

- *Nab assay*

A competitive ligand binding ECL-assay was developed to detect neutralising anti-pegcetacoplan antibodies in human serum samples. The assay was applied in studies 101, 302 and 204.

Pharmacodynamics markers

Analytical methods were developed for three PD biomarkers measured in clinical studies: AH50/AP50, CH50 and C3, at several different laboratories. The methods are considered adequately validated for the purpose.

Flow cytometry assessment was used in studies with PNH subjects (CP0514, 204, 202 and 302) for the characterization of PNH associated abnormal red blood cells or characterization of PNH associated abnormal white blood cells in peripheral whole blood, developed. The validation results for both assays met the acceptance criteria and the assays are considered appropriately validated for the purpose.

PK data across the studies were analysed using non-compartmental and population PK analysis.

Population PK analysis (APL-EX20-CP-002)

Population PK analysis included pegcetacoplan serum concentration-time data from 10 studies. The final analysis dataset included a total of 239 unique subjects with a total of 4377 PK samples, including 3734 quantifiable samples.

Approximately half of subjects in the dataset were adults with PNH (48.1%) and half were healthy volunteers (51.9%). More than half of all subjects were male (56.5%), while 43.5% of subjects were female. The majority of subjects (64.4%) were White and 22.2% of subjects were Asian (including Japanese ethnicity). For all subjects, the median age was 35 years (range: 19-81 years) and median baseline body weight was 71.2 kg (range: 42.3-156 kg).

Pegcetacoplan PK following SC or IV administration was adequately described by a one-compartment disposition model with transit compartment absorption (n=1) for the SC route, direct administration of intravenous doses into the central compartment, and first order elimination. The base model included the following structural covariates: lyophilized formulation (FORM4) on subcutaneous bioavailability (F1), C3 level on CL and V2, and PNH patient status divided into Phase 1 or 2 (PNH2) and Phase 3 studies (PNH3) on CL. In the covariate model evaluation, after stepwise backward elimination procedure based on the likelihood ratio test, weight was found to be a significant covariate on CL/F and V/F.

Parameters for the final model are summarized in Table 5.

Table 3 Pharmacokinetic Parameter Estimates for the Final Model

Theta / Parameter (Units)	Estimate	ASE	%RSE	95% CI
1 CL (L/hr)	0.0124	0.000612	4.94	(0.0112, 0.0136)
2 V2 (L)	4.10	0.204	4.99	(3.70, 4.50)
3 KA (hr^{-1})	0.0394	0.00143	3.64	(0.0366, 0.0422)
4 F1	0.766	0.0394	5.14	(0.689, 0.843)
8 Lyophilized Formulation on F1	0.236	0.0388	16.5	(0.160, 0.312)
9 C3 on CL (g/L)	-0.122	0.0135	11.0	(-0.149, -0.0957)
10 C3 on V2 (g/L)	-0.0740	0.0147	19.8	(-0.103, -0.0452)
11 PNH Phase 1 and 2 on CL	0.534	0.0609	11.4	(0.415, 0.653)
12 PNH Phase 3 on CL	0.346	0.0349	10.1	(0.277, 0.414)
16 WT on CL	0.536	0.0715	13.3	(0.396, 0.676)
28 WT on V2	0.875	0.0887	10.1	(0.701, 1.05)
Residual Variability (%)				
5 RE Healthy Subjects	19.7	0.312	1.58	(19.1, 20.3)
6 RE PNH Phase 1 and 2	32.0	0.979	3.05	(30.1, 34.0)
7 RE PNH Phase 3	11.3	0.385	3.40	(10.6, 12.1)
IIV (CV%)				
ETA1 – CL	19.5			(17.4, 21.4)
ρ(ETA1-CL, ETA2-V2)	0.640			
ETA2 – V2	21.5			(18.8, 24.0)
ETA3 – KA	46.4			(41.1, 51.2)
OFV	-6802.28			

ASE = asymptotic standard error; %RSE = percent relative standard error, 95% CI = 95 percent confidence interval; CL = clearance; V2 = volume of the central compartment; KA = first-order absorption rate constant; F1 = subcutaneous bioavailability; RE = proportional residual error; PNH = patients with paroxysmal nocturnal hemoglobinuria; Phase 1 and 2 =Phase 1 and 2 patient studies; Phase 3 = Phase 3 patient studies; C3 = complement component C3; WT = body weight; IIV = inter-individual variability; CV = approximate coefficient of variation; OFV = objective function value

The model was used to describe PK of pegcetacoplan and to assess effect of the covariates on the variability in PK parameters. Model based simulations were performed to assess the impact of covariates on predicted pegcetacoplan exposure. Stochastic simulations were performed to predict key PK parameters and exposure measures for healthy adults and adult PNH patients. Various SC dosing regimens were simulated reflecting those used in patient studies during the clinical development of pegcetacoplan: 270 mg once daily, 360 mg once daily, 1080 mg twice weekly, and 1080 mg every three days.

Absorption

In studies CP0713-1 and CP1014, pegcetacoplan was administered as SC injections, while later (Study 101) dose was delivered by SC infusion due to dose volume. The change of the mode of administration did not influence the disposition profile of pegcetacoplan.

PK evaluation in healthy subjects showed that following a single SC dose (Study CP0713-1), pegcetacoplan is slowly absorbed with a median Tmax ranging from 108 to 144 hours (4.5 to 6 days).

Following multiple dosing to healthy subjects in Study 101, median Tmax was observed between 576.1 and 647.9 hours (24 to 27 days).

Distribution

No plasma protein binding study has been conducted because pegcetacoplan binds to complement C3 in systemic circulation. Both pegcetacoplan and C3 levels have been monitored in all clinical pharmacology studies.

No specific studies of distribution to red blood cells have been performed. Considering the structure of pegcetacoplan (2 identical cyclic peptides linked by a linear 40 kDa PEG moiety), the potential for distribution in RBCs is considered to be low.

The Vz/F values ranged from 3.6 to 6.1 L across studies (CP0713-1 and CP1014). In the Pop PK analysis, volume of the central compartment for a typical subject was estimated at 4.1 L (21.5%).

Elimination

Pegcetacoplan is composed of 2 identical pentadecapeptides covalently bound to the ends of a linear 40-kDa polyethylene glycol (PEG) molecule. Like other PEGylated protein/peptide conjugates, catabolic pathways are expected to be mainly responsible for the metabolism of pegcetacoplan, which is expected to be degraded into smaller peptide-PEG conjugates, peptides, and eventually amino acids by endogenous proteases. Peptides are known to be metabolized by proteolytic degradation and eliminated by cellular uptake or renal filtration. PEG molecules >5 kDa typically undergo minimal metabolism and are renally excreted.

CL/F, Vz/F and t1/2 in healthy subjects were consistent across the doses and across single and multiple dose studies. The CL/F values in healthy subjects ranged from 11.1 to 20.7 mL/h across studies (CP0713-1 and CP1014). Median t1/2 values ranged from approximately 8 to 10 days (CP0713-1 and 101).

In the Pop PK analysis, clearance for a typical subject was estimated at 12.4 mL/h (19.5%).

Dose proportionality and time dependencies

Following single ascending doses of SC pegcetacoplan from 45 to 1440 mg in healthy subjects (CP0713-1) and multiple ascending doses from 30 to 270 mg once daily during 28 days (CP1014), exposure metrics of AUC and Cmax increased in a generally proportional manner.

Following multiple dosing for 28 days in healthy subjects (CP1014), pegcetacoplan did not show time-dependent PK compared to single dose.

Special populations

Renal impairment

Study 205 evaluated PK of a single 270 mg SC dose of pegcetacoplan in subjects with severe renal impairement compared to matched (sex, age and weight) healthy controls. Geometric means for Cmax (38.2 and 38.7 µg/mL, respectively) and AUC0-∞ (18,153 and 20,078 µg·h/mL, respectively) were similar for subjects in the severe and control groups, as were mean values for CL/F, Vz/F, and t½. Study results show that there were no meaningful differences in PK parameters between control group and group with severe renal impairment.

Additionally, the CrCL was tested as a continuous covariate in the developed PPK model. CrCL was not identified as a significant covariate.

Hepatic impairment

No specific studies have been conducted in study participants to determine the effect of hepatic impairment on the PK of pegcetacoplan. Metabolism of the peptide moiety of the drug molecule is expected to be driven by catabolism to amino acids. PEG moiety is typically renally excreted.

Gender

Based on the results of the pop PK analysis, gender did not have clinically relevant effect on the pegcetacoplan PK.

Race

Study 102 was designed to bridge PK data from non-Japanese healthy volunteers and Japanese subjects. Results from non-Japanese subjects were obtained from SAD study (APL-CP0713-1) and were compared with the results from this part of the study where only Japanese subjects were enrolled.

Results from the two studies over a period of 1008 hours post-dose, showed similar Cmax in both populations (range of 29% higher to 13% lower) across dose range. AUC0-inf geometric means were slightly higher with the Japanese subjects for all of the doses (11 to 36%). This result was supported by Ad–hoc covariate analysis in popPK which showed that covariate ethnicity was not found to have a statistically significant effect on CL.

Weight

PopPK analysis showed that only body weight had an effect on CL and V. Both CL and V2 increased with increasing body weight leading to lower pegcetacoplan exposure with higher body weight; however, the impact on exposure was modest over the range of body weights in the simulation.

Steady-state pegcetacoplan exposure, based on average (Cavg,ss) and maximal (Cmax,ss) concentration, was predicted to be approximately 15% higher at the 5th percentile of body weight (54 kg) and 15% lower at the 95th percentile of body weight (95 kg), compared to a reference weight of 70 kg. Observed impact was found not to have clinically meaningful effect.

Elderly

Based on the results of the pop PK analysis, age did not have clinically relevant effect on pegcetacoplan PK and on model predicted Cavg,ss and Cmax,ss in PNH patients.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	9/147	0/147	0/147

[a] Includes studies CP0713, 401, CP1014, 101, 102 and 205

Pharmacokinetic interaction studies

Only *in vitro* interaction studies were performed.

Pegcetacoplan concentrations evaluated in the *in vitro* studies (up to 6 mg/mL) covered the expected *in vivo* exposure. At concentrations tested, pegcetacoplan was not a direct nor time-dependent inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. Pegcetacoplan was not an inducer of CYP1A2, CYP2B6 and CYP3A4/5.

At concentrations tested, pegcetacoplan was not a substrate or inhibitor of uptake transporters OAT1, OAT3, OCT2, OATP1B1 and OATP1B3, and was not a substrate or inhibitor of efflux transporters P-gp and BCRP**.**

Population PK analysis evaluated the potential interaction between eculizumab and pegcetacoplan since these two agents were co-administered to PNH subjects in Study APL2-302 and Study CP0514. Eculizumab co-administration was not a statistically significant covariate on pegcetacoplan PK parameters.

2.6.2.2. Pharmacodynamics

Mechanism of action

The peptide moieties of pegcetacoplan molecule bind to complement protein C3 and its activation fragment C3b with high affinity, thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation. Pegcetacoplan exerts broad regulation of the complement cascade by acting proximal to both C3b and MAC formation, thereby controlling the mechanisms that lead to EVH and IVH. These functions of Pegcetacoplan underly the observed sustained reduction in complement mediated haemolytic activity in patients with PNH.

Primary and Secondary pharmacology

Primary pharmacology

Healthy patients

The applicant conducted five studies (Study CP0713-1; Study 401; Study CP1014; Study 101; and Study 102) in healthy subjects to evaluate the PD of pegcetacoplan.

No effect on complement CH50 was observed with pegcetacoplan.

Across Study 401 and Study 101, mean AH50 results markedly decreased in all active study drug groups after initiation of treatment. However, in healthy Japanese subjects in Study 102, no statistical significant effect on AH50 in comparison to placebo was observed with pegcetacoplan. A reduction of AP50 from baseline level was observed at the pegcetacoplan 1440 mg dose level in study CP0713-1 and at the pegcetacoplan 180 and 270 mg dose levels in Study CP1014.

Serum complement C3 increased with increasing does in all five studies.

In Study 401, a statistically significant decrease of C3a was observed with pegcetacoplan administration and was not dose-related. However, no effect was observed on C3a with pegcetacoplan administration in Study 101 and Study 102.

In Study CP1014, reduction of LDH compared to placebo was statistically significant and was observed at the 180 and 270 mg dose levels.

Patients with PNH

Study CP0514

Pegcetacoplan demonstrated clinically meaningful improvements in hematologic parameters (e.g., Hb and LDH levels) with a SC dose of 270 mg/day in combination with eculizumab. However, three of four subjects transitioned to pegcetacoplan monotherapy during the study required a further increase in dose to 360 mg/day (1 of these 3 subjects needed a further increase of the equivalent of 440 mg/day) to maintain their hematologic response.

In Cohort 4, an increase in Type III cells as a proportion of the clonal distribution of total RBCs was observed in all 6 subjects.
By Week 13, all Cohort 4 subjects had a decrease in C3 deposition on pooled Type II and III cells. This decrease was maintained for the 4 remaining Cohort 4 subjects through Week 105 (2 years of treatment) with some intermittent fluctuations.
No consistent effect on C3 levels was observed following single dose of pegcetacoplan. All subjects in Cohorts 2, 3, and 4 had dose-related increases in C3 complement during multiple dosing.

Study APL2-302

During the run-in period there was a decrease in Type I PNH and Type II PNH RBCs, and an increase in Type III PNH RBCs. These changes were maintained in the pegcetacoplan treatment group but not the eculizumab treatment group during the RCP.
The C3 levels increased with repeated dosing of pegcetacoplan. The mean C3 concentration at week 2 increased by approximately 280% than baseline level and remained at similar level towards Week 16 (from 0.942 g/L at baseline to 3.826 g/L at Week 16; CFB of 2.824 g/L). In the eculizumab group the C3 levels increased from baseline to Week 2, but then decreased to below baseline at Week 16 (CFB of −0.006 g/L).

Study 202

In all subjects of this study, the applicant found an increase from baseline in clonal distribution of types II + III PNH RBCs.
Noticeable decrease of C3 deposition on types II + III RBCs and C3 deposition on type III RBCs from respective baselines were observed in 2 subjects.
Pegcetacoplan demonstrated clinically meaningful improvements in hematologic parameters (eg, Hb and LDH levels).

C3 levels increased from baseline in all subjects and peaked at approximately Day 43, then remained relatively stable, generally at a level of 200% or more than baseline, for the duration of the study.

Study 204

The sum of the mean clonal distributions of PNH RBCs (percentage of PNH Type II + Type III) was close to 84% of overall PNH RBCs when approaching Day 365.
The proportion of PNH granulocytes and monocytes was minimally changed during the course of the study.
Further supporting the intended pharmacological activity of pegcetacoplan, C3d deposition on Type II and Type III RBCs was decreased after pegcetacoplan treatment.

Pegcetacoplan administration demonstrated improvements in hematologic parameters (e.g., Hb and LDH levels).

C3 concentrations increased with repeated dosing of pegcetacoplan. Change from baseline in mean C3 was 2.310 g/L at Day 29, 2.921 g/L at Day 85, and 2.483 g/L at Day 365. Mean C3 concentrations at Day 29 increased by approximately 250% versus baseline level. C3 subsequently remained at a similar level as observed serum C3 concentrations generally overlapped from Day 29 to Day 365.

<u>Cross-Study comparison of complement PD biomarkers in Studies in subjects with PNH</u>

CH50

There was no meaningful effect of pegcetacoplan treatment on CH50 values in all four studies in subjects with PNH (Study APL2-302, Study 204, Study CP0514, and Study 202) (Table 6).

Table 4: CH50 Absolute Value and Change From Baseline by Visit For Study APL2-302, Study 204, Study CP0514, and Study 202

	Study APL2-302 (RCP)	Study 204	Study CP0514 (Cohort 4)	Study 202
	Pegcetacoplan 1080 mg twice weekly[a] N = 41 (U/mL)	Pegcetacoplan 270 mg/d[b] N = 20 U	Pegcetacoplan 270 mg/d[c] N = 6 (U Eq/mL)	Pegcetacoplan 270 mg/d[b] N = 4 (U Eq/mL)
Baseline, mean (SD)	7.51 (15.81)	589.0 (91.75)	4.8 (9.22)	58.1 (18.32)
Day 15 (n)		19	6	4
Mean (SD)	Not reported	566.9 (50.25)	3.0 (4.56)	42.6 (15.63)
Mean CFB (SD)		-18.5 (57.66)	-1.8 (11.86)	-15.53 (10.36)
Day 29 (n)	40	20	6	4
Mean (SD)	71.94 (52.57)	583.2 (70.10)	3.7 (5.39)	39.0 (20.17)
Mean CFB (SD)	64.33 (48.85)	-5.9 (89.17)	-1.2 (6.79)	-19.2 (7.38)
Day 43 (n)		18	5	4
Mean (SD)	Not reported	583.8 (54.20)	3.6 (5.37)	35.8 (16.98)
Mean CFB (SD)		-11.1 (78.94)	2.4 (6.84)	-22.3 (9.71)
Day 57 (n)	37	17	6	4
Mean (SD)	105.77 (27.54)	597.1 (101.14)	0.2 (0.41)	31.8 (9.13)
Mean CFB (SD)	98.32 (28.63)	3.4 (60.09)	-4.7 (9.33)	-26.3 (10.85)
Day 85 (n)		17	6	4
Mean (SD)	Not reported	572.4 (58.05)	0.2 (0.41)	40.4 (18.93)
Mean CFB (SD)		-22.4 (81.15)	-4.7 (9.33)	-17.7 (9.34)
Day 113 (n)	36	18	6	4
Mean (SD)	118.20 (28.15)	578.2 (104.82)	0.3 (0.82)	40.5 (17.70)
Mean CFB (SD)	110.53 (27.28)	-16.7 (102.03)	-4.5 (9.46)	-17.6 (7.48)
Day 141 (n)		18	6	4
Mean (SD)	NA	587.2 (69.98)	0.2 (0.41)	43.9 (15.50)
Mean CFB (SD)		-7.7 (69.61)	-4.7 (9.33)	-14.3 (13.76)
Day 169 (n)		18	6	4
Mean (SD)	NA	583.2 (103.33)	0.2 (0.41)	43.3 (17.89)
Mean CFB (SD)		-11.7 (93.95)	-4.7 (9.33)	-14.8 (11.05)
Day 365 (n)		17	2	4
Mean (SD)	NA	569.0 (72.38)	0.5 (0.71)	48.8 (14.40)
Mean CFB (SD)		-30.5 (68.10)	-2.5 (4.95)	-9.3 (5.42)

Abbreviations: CFB = change from baseline; NA = not applicable; RCP = randomized controlled period.
[a] Dates are relative to the start of the 16-week RCP. Dose could be increased to 1080 mg 3 times weekly if clinically indicated.
[b] Study duration was up to 365 days. Dose could be increased to 360 mg/day if clinically indicated. Subjects were naive to C5 inhibitor treatment.
[c] Cohort 4 only. Dose could be increased to 360 mg/day if clinically indicated; one subject was granted approval to receive 360 mg/day, with a dose of 720 mg every 4th day (equivalent to approximately 440 mg/day). Subjects received pegcetacoplan as an add-on to C5 inhibitor treatment.
Sources: Study APL2-302 Table 14.3.7.3.2, Study 204 Table 14.2.8.1; Study CP514 Table 14.2.8.1, Appendix 5.3, Table 7.

AH50/AP50

A reduction of AP50 from baseline level was observed with pegcetacoplan treatment in both Study 204 and Study 202 that evaluated treatment-naïve subjects with PNH. A maximum decrease of approximately 70% from baseline was observed at Day 29 in Study 204, while mean observed AP50 level subsequently recovered to approximately half of the baseline value at Day 169 and remained at a similar level at Day 365. Individual variations were noted in AP50 percentage throughout the Study 202. However, all subjects experienced a decrease from baseline in AP50 through to Day 365.

Low AH50 values at baseline in Study CP0514 and Study APL2-302 were consistent with prior and concomitant treatment with eculizumab, a strong inhibitor of both classical and alternative pathway complement hemolytic activity. AH50 increased with the cessation of eculizumab in both studies. Subjects in Study CP0514 received co-administration of eculizumab and pegcetacoplan for a long period of time and no further effect on AH50 as a result of pegcetacoplan treatment could therefore be determined in the single-dose phase or in the multiple-dose phase until after 1 year of treatment. Subjects randomized to the pegcetacoplan group of Study APL2-302 discontinued eculizumab treatment

after the run-in period. The AH50 values of these subjects also increased toward normal, although the value stayed close to 50% of normal at Week 16 (or Day 113).

Table 5: AH50/AP50 (U/mL) Absolute Value and Change From Baseline by Visit for Study APL2-302, Study 204, Study CP0514, and Study 202

	Study APL2-302 (RCP)	Study 204	Study CP0514 (Cohort 4)	Study 202
	Pegcetacoplan 1080 mg twice weekly[a] N = 41	Pegcetacoplan 270 mg/d[b] N = 20	Pegcetacoplan 270 mg/d[c] N = 6	Pegcetacoplan 270 mg/d[b] N = 4
Baseline, mean (SD)	37.2 (22.3)	0.84 (0.269)	35.0 (0.00)	3.0 (0.81)
Day 15 (n)			6	4
Mean (SD)	Not reported	Not reported	39.2 (10.21)	1.1 (0.19)
Mean CFB (SD)			4.2 (10.21)	-1.8 (0.92)
Day 29 (n)	40	19	6	4
Mean (SD)	53.2 (45.3)	0.24 (0.208)	43.7 (21.23)	1.6 (0.25)
Mean CFB (SD)	16.4 (37.28)	−0.60 (0.241)	8.7 (21.23)	-1.4 (0.78)
Day 43 (n)			5	4
Mean (SD)	Not reported	Not reported	35.00 (0.00)	1.4 (0.40)
Mean CFB (SD)			0.0 (0.00)	-1.5 (0.89)
Day 57 (n)	37		6	4
Mean (SD)	62.7 (43.90)	Not reported	35.0 (0.00)	1.3 (0.41)
Mean CFB (SD)	26.2 (33.98)		0.0 (0.00)	-1.7 (1.12)
Day 85 (n)		17	6	4
Mean (SD)	Not reported	0.29 (0.302)	35.0 (0.00)	1.6 (0.69)
Mean CFB (SD)		−0.54 (0.277)	0.0 (0.00)	-1.39 (0.99)
Day 113 (n)	36		6	4
Mean (SD)	66.2 (46.60)	Not reported	35.0 (0.00)	1.4 (0.79)
Mean CFB (SD)	29.4 (42.82)		0.0 (0.00)	-1.6 (1.42)
Day 141 (n)			6	4
Mean (SD)	NA	Not reported	35.0 (0.00)	1.6 (0.48)
Mean CFB (SD)			0.0 (0.00)	-1.4 (1.12)
Day 169 (n)		18	6	4
Mean (SD)	NA	0.41 (0.327)	35.0 (0.00)	1.6 (0.37)
Mean CFB (SD)		−0.44 (0.325)	0.0 (0.00)	-1.3 (1.02)
Day 365 (n)		16		4
Mean (SD)	NA	0.46 (0.412)	Not reported	2.2 (0.71)
Mean CFB (SD)		−0.39 (0.314)		-0.81 (0.45)

Abbreviations: AH50/AP50 = alternative complement pathway hemolytic activity assay; CFB = change from baseline; NA = not applicable; RCP = randomized controlled period.

[a] Dates are relative to the start of the 16-week RCP. Dose could be increased to 1080 mg 3 times weekly if clinically indicated.

[b] Study duration was up to 365 days. Dose could be increased to 360 mg/day if clinically indicated. Subjects were naive to C5 inhibitor treatment.

[c] Cohort 4 only. Dose could be increased to 360 mg/day if clinically indicated; one subject was granted approval to receive 360 mg/day, with a dose of 720 mg every 4th day (equivalent to approximately 440 mg/day). Subjects received pegcetacoplan as an add-on to C5 inhibitor treatment.

Source: Study APL2-302 Table 14.3.7.3.2, Study 204 Table 14.2.8.2, Study CP0514 Table 14.2.8.2, Appendix 5.3, Table 6.

C3

Across all 4 studies with PNH subjects, C3 levels increased after pegcetacoplan dosing and maintained at a level that was more than 200% than baseline values from Day 43 through the rest of respective treatment period, indicating robust and sustained target C3 engagement (

Table **8**).

Table 6: C3 (g/L) Absolute Value and Change From Baseline by Visit for Study APL2-302, Study

204, *Study CP0514, and Study 202*

	Study APL2-302 (RCP)	Study 204	Study CP0514 (Cohort 4)	Study 202
	Pegcetacoplan 1080 mg twice weekly[a] N = 41	Pegcetacoplan 270 mg/d[b] N = 20	Pegcetacoplan 270 mg/d[c] N = 6	Pegcetacoplan 270 mg/d[b] N = 4
Baseline, mean (SD)	0.94 (0.27)	0.91 (0.20)	1.06 (0.21)	1.10 (0.14)
Day 15 (n)	35	19	6	4
Mean (SD)	3.60 (0.73)	2.34 (0.52)	1.63 (0.22)	2.6 (0.36)
Mean CFB (SD)	2.58 (0.57)	1.45 (0.37)	0.57 (0.16)	1.50 (0.26)
Day 29 (n)	38	20	6	3
Mean (SD)	3.64 (0.71)	3.22 (0.50)	2.96 (0.46)	4.1 (0.40)
Mean CFB (SD)	2.65 (0.62)	2.31 (0.38)	1.89 (0.48)	3.0 (0.46)
Day 43 (n)	37	18	5	4
Mean (SD)	3.71 (0.65)	3.50 (0.73)	3.60 (0.82)	5.0 (0.82)
Mean CFB (SD)	2.73 (0.63)	2.57 (0.56)	2.51 (0.89)	3.9 (0.85)
Day 57 (n)	32	17	6	4
Mean (SD)	3.70 (0.81)	3.59 (0.68)	3.46 (1.34)	4.8 (0.13)
Mean CFB (SD)	2.75 (0.68)	2.68 (0.55)	2.40 (1.28)	3.7 (0.24)
Day 85 (n)	38	17	6	4
Mean (SD)	3.80 (0.78)	3.86 (0.67)	4.07 (0.74)	4.6 (0.06)
Mean CFB (SD)	2.82 (0.71)	2.92 (0.54)	3.01 (0.73)	3.5 (0.17)
Day 113 (n)	34	18	6	4
Mean (SD)	3.83 (0.74)	3.70 (0.58)	4.00 (0.61)	4.2 (0.17)
Mean CFB (SD)	2.82 (0.61)	2.77 (0.47)	2.94 (0.63)	3.1 (0.24)
Day 141 (n)		18	6	4
Mean (SD)	NA	3.74 (0.61)	4.11 (0.71)	4.1 (0.35)
Mean CFB (SD)		2.82 (0.48)	3.04 (0.72)	3.0 (0.31)
Day 169 (n)		18	6	4
Mean (SD)	NA	3.62 (0.61)	4.08 (0.87)	4.1 (0.35)
Mean CFB (SD)		2.70 (0.52)	3.02 (0.89)	3.0 (0.31)
Day 365 (n)		17	3	4
Mean (SD)	NA	3.42 (0.70)	3.95 (0.80)	4.0 (0.28)
Mean CFB (SD)		2.48 (0.72)	2.99 (0.63)	2.9 (0.22)

Abbreviations: CFB = change from baseline; NA = not applicable; RCP = randomized controlled period.
[a] Dates are relative to the start of the 16-week RCP. Dose could be increased to 1080 mg 3 times weekly if clinically indicated.
[b] Study duration was up to 365 days. Dose could be increased to 360 mg/day if clinically indicated. Subjects were naive to C5 inhibitor treatment.
[c] Cohort 4 only. Dose could be increased to 360 mg/day if clinically indicated; one subject was granted approval to receive 360 mg/day, with a dose of 720 mg every 4th day (equivalent to approximately 440 mg/day). Subjects received pegcetacoplan as an add-on to C5 inhibitor treatment.
Sources: Study APL2302 Table 14.3.7.3.2, Study 204 Table 14.2.8.3, Study CP0514 Table 14.2.8.3, Appendix 5.3, Table 8.

According to the results of Study CP0514, pegcetacoplan showed pharmacological activity at a daily SC dose dose of 180 mg. The cumulative data of Study 204, Study CP0514 (Cohort 4), and Study 202 (a Phase 2a study) suggested that most subjects (at least 22 of 30) had a clinically significant response with pegcetacoplan at 270 mg/day dose. Six of 30 subjects (20%) required a 360 mg/day dosage or higher to sustain robust clinical response during long-term treatment of pegcetacoplan monotherapy. In Study APL2-302, the Applicant investigated the effectiveness of less frequent dosing regimens, such as twice-weekly dosing. On the basis of preliminary PK modelling, a twice weekly dose of 1080 mg was selected.

The effect of pegcetacoplan on cardiac conduction

Data are not available for a situation that may pose a risk for a suprapharmacologic exposure of pegcetacoplan, such as a potential drug-drug interaction. Based on the class and structure of the molecule, the Applicant does not expect drug-drug interactions. In addition, since the excretion of pegcetacoplan is almost entirely renal, the Applicant also does not expect that hepatic insufficiency to increase pegcetacoplan exposure.

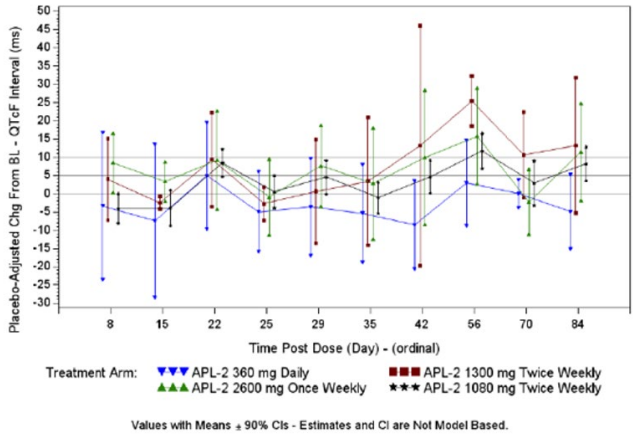
APL2-101

There appears to be no large effect of pegcetacoplan on heart rate. No subjects met bradycardic or tachycardic outlier criteria. These findings are of no clinical significance.

No signal of a clinically significant effect on PR was observed with pegcetacoplan. No subjects met PR outlier criteria.

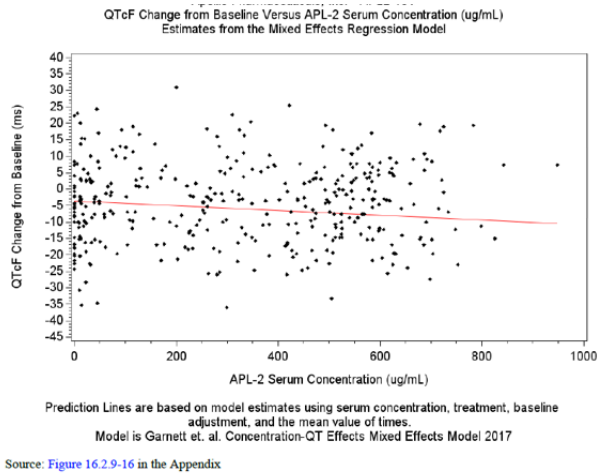
No signal of a clinically significant effect on QRS was observed with pegcetacoplan. No subjects met QRS outlier criteria.

The placebo corrected QTcF change from baseline ranged from -8.6 ms in the 360 mg daily treatment group (Day 42) to 25.4 ms in the 1300 mg twice-weekly treatment group (Day 56). In the group with the largest sample size, the 1080 mg twice weekly treatment group, the largest value for ΔΔQTcF was 15.8 ms (90% 2-sided upper confidence bound 29.0 ms) on Day 56 (n=20). Given the very small sample sizes of these cohorts (generally only 4 subjects to start other than in the 1080 mg weekly treatment group), these data are difficult to interpret (Figure 3 and Figure **4**).



Source: Figure 16.2.9-8 in the Appendix

Figure 3. QTcF Interval: Placebo-Adjusted Mean Change from Baseline (APL-EX20-CP-004; Figure 12)



Source: Figure 16.2.9-16 in the Appendix

Figure 4. QTcF Change from Baseline vs Pegcetacoplan Serum Concentration (APL-EX20-CP-004, Figure 16)

One subject developed nonspecific ST depression that did not appear to be clinically significant.

APL2-302

The timepoint analysis demonstrated no clinically significant effect of pegcetacoplan or eculizumab on heart rate. No patients met bradycardic outlier criteria, while one patient in the eculizumab treatment met tachycardic outlier criteria.

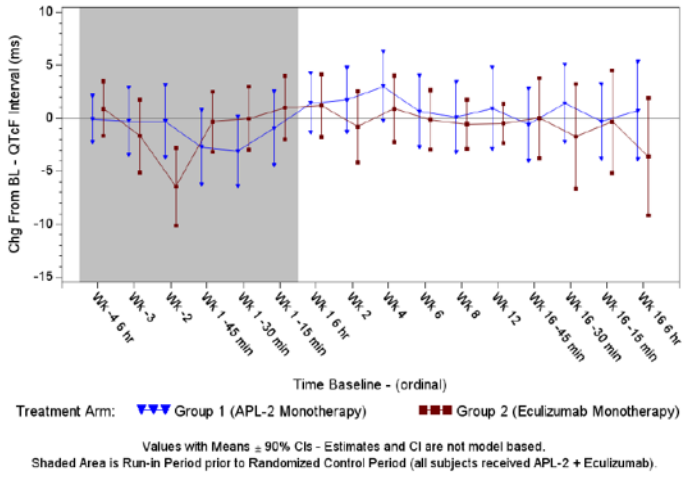
The timepoint analysis demonstrated no clinically significant effect of pegcetacoplan or eculizumab on PR interval. No patients met PR outlier criteria.

The timepoint analysis demonstrated no clinically significant effect of pegcetacoplan or eculizumab on QRS duration. No patients met QRS outlier criteria.

The mean changes from baseline for QTcF for the pegcetacoplan and ecluizumab treatment groups during the RCP ranged from -0.6 to 1.7 and -3.6 to 1.2 ms respectively; these results are of no clinical relevance.

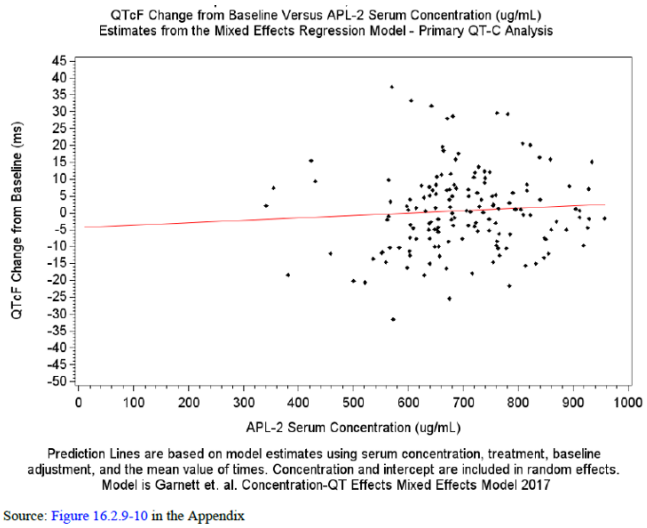
None of the timepoints for the pegcetacoplan or eculizumab groups demonstrated a 90% two sided upper bound for QTcF change from baseline that approached or exceeded 10 ms, demonstrating no signal of any effect of pegcetacoplan on cardiac repolarization. During the RCP, the highest QTcF change from baseline in the pegcetacoplan treatment group was 3.0 ms (UCL 4.8 ms). For the eculizumab treatment group, the highest QTcF change from baseline was 0 ms (UCL 6.3 ms). These findings are of no clinical significance (Figure 5).

Figure 5. QTcF Interval: Mean Change From Baseline (APL-EX20-CP-004, Figure 7)



Source: Figure 16.2.9-8 in the Appendix

The results of the PK-PD model show that the slope of the relationship between ΔQTcF and pegcetacoplan serum concentration was flat to slightly positive (P=0.5151) and the overall predicted baseline corrected value at the mean C_{max} for pegcetacoplan was 1.4 ms (90% 2-sided UCI 2.9 ms). There was a substantial negative intercept, probably related to the lack of low pegcetacoplan serum concentrations (Figure **6**).



Source: Figure 16.2.9-10 in the Appendix

Figure 6. QTcF Change from Baseline vs Pegcetacoplan Serum Concentration (APL-EX20-CP-004, Figure 14)

In all of the additional sensitivity PK-PD analyses, each of which included samples collected near the initiation of pegcetacoplan treatment (during the Run-in Period), the relationship between ΔQTcF and pegcetacoplan serum concentration was flat. With the inclusion of data when pegcetacoplan serum concentrations were 0 or low, the intercepts were all small. The model predicted mean ΔQTcF (Sensitivity Analyses 1 and 2) or ΔΔQTcF (Sensitivity Analysis 4) values were all <0 ms, with 90% 2-sided upper confidence bounds below 4 ms (Table 9).

Table 7: Change from Baseline versus the Pegcetacoplan Serum Concentration - Predicted from Mean Cmax [1,2,3] QTcF Interval (msec), Pegcetacoplan (µg/mL) Pharmacokinetic-Pharmacodynamic Population in Study APL2-302: Sensitivity C-QTc Analyses

Sensitivity Analysis Number	Treatment Dose [1]	Geometric Mean C_{max} (µg/mL) [2]	Predicted Mean Effect at Mean C_{max} [3] (ms)	Lower CI[3] (ms)	Upper CI[3] (ms)
1	Pegcetacoplan 1080 mg twice weekly	720.0	-1.548	-7.106	3.808
2	Pegcetacoplan 1080 mg twice weekly	720.0	1.249	-0.589	3.214
4	Pegcetacoplan 1080 mg twice weekly	720.0	0.089 [4]	-2.200 [4]	2.400 [4]

[1] Linear Mixed Effects Model is fit for change from baseline versus the serum concentration on a linear scale, with time (categorical), baseline adjustment, and fixed and random effects for the intercept. Concentration could not be included in random effects.
[2] Mean Cmax is is provided by Sponsor (Apellis) based on APL-2 serum concentration data in Study APL2-302 (up to Week 16).
[3] Confidence Intervals are based on bootstrap methodology using percentile confidence intervals of 1000 replicates.
Lower/Upper Confidence = upper one-sided 95% linear mixed model based confidence limit, based on bootstrap methods using percentile confidence intervals, using 1000 replicates. Predicted means based on bootstrapped estimates.
[4] For Sensitivity Analysis 4, values are displayed for placebo corrected QTcF change from baseline (ΔΔQTcF).
Source: Table 14.3.4.4-25b and 14.3.4.4-26b in the Appendix

Several patients developed new, minor ECG morphologic findings in this study. In the pegcetacoplan treatment group, two patients developed new T wave inversion, and one patient developed new ST segment depression (< 0.1 mV). A review of these ECGs demonstrated only nonspecific ST and T wave changes that were not suggestive of ischemia or pericardial process, and which did not appear to be clinically significant.

PD interactions

Concomitant treatment with pegcetacoplan and eculizumab had no meaningful impact on CH50 relative to baseline and had negligible impact on AH50/AP50 relative to baseline. According to the Applicant, the

pharmacological effect on CH50 and AH50/AP50 of both drugs is largely overlapping with limited additive effects.

Relationship between plasma concentration and effect

A sigmoidal Emax direct effect model described the pegcetacoplan concentration and Hb/LDL level in subjects with PNH.

Exposure Relationship to Hemoglobin Response in Subjects With PNH

The most common pegcetacoplan dosing regimens were 1080 mg twice weekly (81 subjects) or 270 mg once daily (30 subjects) with sorbitol (81 subjects) or dextrose (26 subjects) formulations. Hb level increases with increasing pegcetacoplan concentration, but that the relationship is non-linear over the range of pegcetacoplan concentrations in the observed data.

The maximal effect was a 36.3% increase from baseline with an EC_{50} of 272 µg/mL the sigmoidal relationship is steep over the observed pegcetacoplan concentration range (Hill coefficient of 5.85).

The E-R analyses showed that 270 mg/day and 1080 mg SC twice-weekly dosing regimen are both effective for improving Hb in subjects with PNH. Exposure from 270 mg/day dosage is expected to achieve at least 95% of the maximal predicted Hb response. However, exposure from 1080 mg twice-weekly dosage is expected to achieve at least 99% of the maximal predicted Hb response.

Individuals with lower baseline Hb values are predicted to have greater Hb response, in terms of proportional increase from baseline. However, individuals with renal impairment are anticipated to have a lesser Hb response than those with normal renal function at baseline.

Exposure Relationship to Lactate Dehydrogenase Response in Subjects with PNH

Median baseline LDH levels were approximately 10-fold higher in eculizumab-naive patients enrolled in Study 202 (2585 IU/L) and Study 204 (2227 IU/L) compared to patients receiving eculizumab at baseline in Study APL2-302 and Study CP0514 (225 IU/L), consistent with the expected pharmacological effect of eculizumab.

For eculizumab treatment-naive patients, the maximal effect of pegcetacoplan was estimated as a 90.8% decrease in LDH level from a baseline of 2117 IU/L with an EC_{50} of 173 µg/mL. 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. A common Hill coefficient was estimated at 3.84 for both conditions, suggesting a steep pegcetacoplan concentration-LDH response relationship over the observed pegcetacoplan concentration range.

Treatment with eculizumab at baseline influenced baseline LDH level, E_{max}, and EC_{50}. As a result, median LDH levels at steady state following pegcetacoplan 1080 mg twice weekly are predicted to be 231 IU/L for eculizumab-naive subjects and 177 IU/L for subjects with prior eculizumab treatment. However, pegcetacoplan 1080 mg twice weekly effectively controls LDH: 78.4% and 97.4% of eculizumab-naive and eculizumab-treated subjects, respectively, achieved LDH levels below 1.5 times the upper limit of normal (ULN = 226 IU/L).
The LDH exposure-response analysis showed that the 270 mg/day and 1080 mg twice-weekly dosing regimen are both effective for LDH response. Exposure from 270 mg/day dosage is expected to achieve at least 90% of the maximal predicted LDH response. However, exposure from 1080 mg twice-weekly dosage is expected to achieve at least 95% and 99% of the maximal predicted LDH response in eculizumab-treated subjects and eculizumab-naive subjects., respectively, with 71.6% of all subjects predicted to achieve LDH levels below the ULN.

LDH levels at steady-state pegcetacoplan concentrations following 1080 mg twice-weekly are predicted to be only 1.25-fold (90% CI: 0.999-1.55) higher in treatment-naive patients than in those with eculizumab treatment at baseline, suggesting that pegcetacoplan monotherapy as initial treatment provides LDH control similar to that of sequential therapy with eculizumab and pegcetacoplan.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics:

Methods

Serum pegcetacoplan concentration

Concentrations of pegcetacoplan (APL2) were determined in human serum using validated a liquid chromatography tandem mass spectrometry (LC-MS/MS) method.

Immunogenicity

- *ADA assay*

In early clinical studies (CP0713, CP1014, 401, CP0514 and 6 subjects from study 204), ELISA-based ADA assay was used to detect antibodies against pegcetacoplan in human serum. The drug tolerance of the assay was very low.

In later clinical studies (101, 205, 102, 202, 204 and pivotal study 302), a standard multi-tiered approach was employed including screening, confirmatory and titer assays to evaluate anti-drug antibodies in accordance with EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1).

In those studies, ECL-based ADA assay was used to detect antibodies against peptide moiety of pegcetacoplan in parallel with ELISA-based ADA assay to detect antibodies against PEG moiety of the drug molecule.

Main issue of both assays for antibodies against pegcetacoplan peptide (BAL-17-143-048-REP and 190339VMES_APWM) was the low drug tolerance which could lead to false negative results.

Anti-pegcetacoplan peptide antibodies are being further evaluated in study 302 at Weeks 32, 48 and during the Follow-up at weeks 54 and 60. The low assay drug tolerance could affect reliability of ADA detection at these time points. Anti-pegcetacoplan peptide antibodies will also be evaluated in study 307, an open-label extension study to evaluate the long-term safety and efficacy of pegcetacoplan in the treatment of PNH. The Applicant will attempt to further improve drug tolerance of the assay used for the analysis of patient samples from studies 302, 307 and 308.

NAb assay

A competitive ligand binding ECL-assay was developed to detect neutralising anti-pegcetacoplan antibodies in human serum samples. All the samples were handled within the validated stability conditions.

Population PK analysis (APL-EX20-CP-002)

The base model included the following structural covariates: lyophilised formulation (FORM4) on subcutaneous bioavailability (F1), C3 level on CL and V2, and PNH patient status divided into Phase 1 or 2 (PNH2) and Phase 3 studies (PNH3) on CL. After stepwise backward elimination procedure based on the likelihood ratio test, weight was found to be a significant covariate on CL/F and V/F. No other significant covariates were identified including race (Japanese vs Caucasian) and ADA (ad-hoc analysis).

All PK parameters, both fixed and random effects, of the final model were estimated with good precision (RSE <20%). IIV estimates were reduced compared to the base model. All GOF plots showed that the model adequately described the observed pegcetacoplan concentrations. The VPCs showed that the model captured the global trend and the variability of the concentration vs time data reasonably well. Therefore, the final population PK model is deemed adequate for simulations.

Absorption

PK evaluation in healthy subjects showed that following a single SC dose (Study CP0713-1), pegcetacoplan is slowly absorbed with a median Tmax ranging from 108 to 144 hours (4.5 to 6 days). This is reflected in the SmPC.

Bioavailability

In the Pop PK analysis, bioavailability of the sorbitol, mannitol and dextrose formulation was estimated to be 76.6%, whereas for the lyophilized formulation the estimation was 94.7%. Bioavailability as obtained by the Pop PK analysis is stated in the SmPC.

The preferred site of administration across the studies was abdomen, but if this site was not well tolerated by the patient, thigh or upper arm could be selected as an alternative. Even limited data are available with injection sites other than abdomen, no clear difference linked to injection site was evidenced. The SmPC allows administration in all three sites.

Bioequivalence

No formal bioavailability or bioequivalence studies were conducted. An inter-study comparison of the dextrose formulation (used in early clinical studies CP1014, 204, CP0514 and CP0713-1) and the acetate buffer–based, sorbitol containing formulation (study 101 and pivotal study 302) showed a similar disposition profile. These are also the two formulations used in the majority of subjects across the clinical development program.

Different formulations were assessed as covariates in the Pop PK model. All formulations (dextrose, mannitol and lyophilized) showed slightly higher predicted Cavg,ss and Cmax,ss than the reference sorbitol formulation, but only 38% higher exposure with lyophilized formulation was deemed significant, which was consistent with higher estimated bioavailability for this formulation. Lyophilized formulation was used in special population studies (102 and 205). Steady-state exposures obtained by dextrose formulation are considered similar to steady-state exposures achieved by the sorbitol formulation. Sorbitol formulation was used in the pivotal study 302 and is planned for commercialisation.

In conclusion, considering the very slow absorption of pegcetacoplan, similar t1/2 between the dextrose and sorbitol formulation and similar steady-state exposures achieved, the absence of formal BE study can be accepted. Moreover, the pivotal study used the sorbitol formulation which is the proposed commercial formulation.

Distribution

In the SmPC section 5.2, the Applicant states predicted volume of distribution for PNH patients based on the PopPK model (3.9 L (CV 35%)). This is considered acceptable.

Elimination

Elimination pathways and metabolism of pegcetacoplan were not specifically studied. The metabolism of the peptide moiety of the drug molecule is expected to be driven by catabolism to amino acids. However, no dedicated investigation of pegcetacoplan metabolism has been made.

With regards to PEG moiety, like other High molecular weight pegylated drugs, the elimination is very slow. The drug clearance equates approximately 0.3% the glomerular filtration rate. However, it was not

agreed that the predominant elimination of the drug product is by renal route. Preclinical study 17MTX-001 was performed in *Cynomolgus* Monkey and investigated 3H-radiolabelled pegcetacoplan (synthesized using [3H]-labeled valine). Therefore, the radiolabeled material recovered in urine is tracing only peptide moiety of pegcetacoplan and could not inform the elimination of the PEG moiety. The following information is implemented in the SmPC (paragraph 5-2 Metabolism/ Elimination): "Based on its PEGylated peptide structure, the metabolism of pegcetacoplan is expected to occur via catabolic pathways and be degraded into small peptides, amino acids, and PEG. Results of a radiolabelled study in *Cynomolgus* monkeys suggest the primary route of elimination of the labelled peptide moiety is via urinary excretion. Although the elimination of PEG was not studied, it is known to undergo renal excretion."

Target population

A population PK model has been developed in order to elucidate the PKs of pegcetacoplan. The population PK analysis (APL EX20-CP-002) predicted lower pegcetacoplan exposure in subjects with PNH compared to healthy subjects. The effective half-life of pegcetacoplan at 1080 mg SC twice weekly was estimated as 8.0 days for adult patients with PNH compared with 10.1 days in healthy subjects, however, the 90% prediction intervals are largely overlapping which is in line with the observed data.

Immunogenicity

Samples from 6 subjects from study 204 tested initially for ADAs were negative and were planned to be re-analysed by a more specific method.

In the later clinical studies, more specific methods were used to detect antibodies against the peptide moiety of the molecule and antibodies against the PEG moiety. Overall, a low frequency of anti-peptide antibodies was observed with 8 out of 177 subjects (4.5%) having a confirmed positive assay result. The interpretation of this result should be taken with care due to low drug tolerance of both assays employed.

On the other hand, a very high proportion of subjects had a confirmed positive assay result for anti-PEG antibodies (145/177, 81.9%). Mostly, this was due to pre-existing anti-PEG antibodies in pre-dose samples. There was a low incidence of treatment-emergent (4.5%) or treatment-boosted (3.4%) anti-PEG antibody response.

Special populations

Renal impairment

According to the study 205 results there were no meaningful differences in PK parameters between control group and group with severe renal impairment. It is agreed that under the experimental conditions of the study, no differences in primary or secondary PK parameters was observed between the severe impaired subjects and the control group. However, the study was conducted after administration of a single 270 mg dose. The tested dose was much lower (1/4) than the claimed unitary 1080 mg dose. The response is solely supported by data from the population-PK analysis. Based on this analysis, where CLcr was tested as a continuous covariate, no significant effect was evidenced. Of note, very few data from patients with severely impaired renal function (1.7 % in respectively severe and end-stage patients) are included in the analyzed dataset. Even in patients with moderately impaired renal function, the available data are rather scarce (6.3 %). The SmPC accordingly states that minimal data are available for patients with renal impairment administered pegcetacoplan 1080 mg twice weekly.

Hepatic impairment

Considering the fact that the product is a peptide; the lack of dedicated studies in subjects with hepatic impairment is justified. It is agreed that a dose adjustment in this patient population is not warranted.

Body weight

PNH patients with body weight below 50 kg (5th percentile in the analysis data set) are predicted to have up to 34% higher Cavg,ss values compared to a reference 70 kg subject. Although not many patients with body weight <50 kg are expected in clinical practice, the impact on safety of this increase in exposure is not known. The SmPC reflects information with regards to the impact of body weight below 50 kg on pegcetacoplan exposure and limited safety information for those patients.

Elderly

Dataset included patients with age range from 19-81 years. Based on the results of the pop PK analysis, age did not have clinically relevant effect on pegcetacoplan PK and on model predicted Cavg,ss and Cmax,ss in PNH patients.

Race/ Ethnicity:

Inter study comparison did not show any meaningful effect of Japanese ethnicity and popPK did not identified race as a significant covariate. However, the conclusion made from this analysis should be sought cautiously as very scarce data are available in non-white patients/subjects (black, Hispanic and Asians). This is reflected in the SmPC.

Pharmacodynamics

Complement C3 levels increased by more than 200% from baseline levels with increasing pegacetoplan dose in multi dose studies. These findings indicate that pegcetacoplan interacts with complement C3.

No effect on complement CH50 was observed with pegcetacoplan.

A reduction of AP50 from baseline level was observed with multiple-dose of pegacetacoplan in Study 202 and Study 204. The results of Study CP5014 and Study APL2-302 showed that pegcetacoplan reduces complement AH50 and demonstrated inferiority of pegcetacoplan versus eculizumab in reducing AH50. The findings for AH50/AP50 suggested that repeated dosing of pegcetacoplan led to a persistent and partial inhibition of alternative complement pathway haemolytic activity.

The Applicant considers that the increase in Type II+III PNH RBCs indicates a reduction in haemolysis, due to protection of the PNH RBCs, and corresponding to the rise in Hb. This is acceptable. In addition, this increase in Type II+III PNH RBCs was higher in pegcetacoplan arm than in eculizumab arm which could show a higher activity of pegcetacoplan compared to eculizumab in the control of haemolysis. However, the impact of pegcetacoplan on PNH RBCs percent Type III (RBC with absent levels of CD55 and CD59) was higher than on PNH RBCs percent Type II (RBC with reduced levels of CD55 and CD59). The Applicant provided a discussion regarding this different impact observed depending on the Type of PNH red blood cells and clarifications are considered acceptable. The Applicant also provided an additional analysis assessing the impact of transfusions and the results are in concordance with those reported in Study APL2-302 16-week CSR.

Pegcetacoplan treatment resulted in the improvement of Hb level and reduction of absolute reticulocyte count, LDH and total bilirubin.

Based on these results, repeated dosing of pegcetacoplan with 270-360 mg daily or 1080 mg twice-weekly leads to control of both intravascular and extravascular haemolysis.

Relationship between plasma concentration and effect

Exposure-response analyses have been conducted for biomarkers of clinical response Hb and LDH. A sigmoidal Emax direct effect model described the pegcetacoplan concentration and Hb/LDL level in subjects with PNH reasonably well.

The maximal effect of pegacetacoplan was estimated as a 36.3% increase in Hb level from baseline with an EC50 of 272 µg/ml. For eculizumab treatment-naive patients, the maximal effect of pegcetacoplan was estimated as a 90.8% decrease in LDH level from a baseline with an EC50 of 173 µg/mL. The maximal effect was a 32.5% decrease from a baseline with an EC50 of 250 µg/mL for subjects on eculizumab treatment at baseline. The E-R analyses showed that 270 mg/day and 1080 mg SC twice-weekly dosing regimen are both effective for improving Hb and control of LDL in subjects with PNH. Exposure from 270 mg/day dosage is expected to achieve at least 95% of the maximal predicted Hb response and at least 90% of the maximal predicted LDH response. However, exposure from 1080 mg twice-weekly dosage is expected to achieve at least 99% of the maximal predicted Hb respon of all PNH subjects and at least 95% and 99% of the maximal predicted LDH response in eculizumab-treated subjects and eculizumab-naive subjects.

The dose and dosing regimens (1080 mg SC twice-weekly) selected for the Phase 3 studies are adequate.

The effect of pegcetacoplan on cardiac conduction

The Applicant did not conduct "Thorough QT/QTc Study". Instead of that study, the applicant performed the analysis (APL-EX20-CP-004) which evaluated the effect of pegacetacoplan on ECG parameters in the Phase 3 Study APL2302 and the Phase 1 Study 101. In addition, the Applicant considered that it was not necessary to evaluate the effect of pegcetacoplan at supratherapeutic doses on the QT interval. These studies were also conducted without a separate positive control group. Study APL2-302 did not have concurrent placebo control group.

The explanation regarding the Applicant's claim that it was not necessary to evaluate the effect of pegcetacoplan at supratherapeutic doses on the QT/QTc interval is acceptable. The lack of a positive control and lack of the placebo control group in Study APL2-302 is drawback for the results interpretation.

According to these analyses, the Applicant concluded that pegcetacoplan has no clear effect on heart rate, PR and QRS interval duration, cardiac repolarization (QT interval corrected for heart rate), or other ECG parameters. In Study 2-302, there no effect on heart rate, PR and QRS interval duration, cardiac repolarization (QTc), or other electrocardiopraphic parameters. However, in Study APL2-101, the placebo corrected QTcF change from baseline was 25.4 ms in the 1300 mg twice-weekly treatment group (Day 56). Then, in the group with the largest sample size, the 1080 mg twice weekly treatment group, the largest value for ΔΔQTcF was 15.8 ms (90% 2-sided upper confidence bound 29.0 ms) on Day 56 (n=20). The Applicant did not interpret the results of Study APL2-101 due to very small sample size of the cohorts in that study. Considering the results of Study APL2-101 (only study with a placebo control) and considering two clinical significant QT prolongations observed in one subject in Study 204, the Applicant provided a discussion on the observed QT/QTc prolongations, possible underlying reasons and further justified the claim that QT prolongation with pegcetacoplan is not expected based on overall available data.

2.6.4. Conclusions on clinical pharmacology

Overall, the clinical pharmacology package available with pegcetacoplan is considered sufficient to support the marketing authorization for the proposed indication.

2.6.5. Clinical efficacy

2.6.5.1. Dose response studies

Early clinical evaluation of repeated dosing of pegcetacoplan in subjects with PNH was conducted in a Phase 1b study (Study CP0514) in subjects receiving treatment with eculizumab. Initially, daily 5-mg (Cohort 1) and 30-mg (Cohort 2) SC doses of pegcetacoplan were tested for 28 days. PK data from the SAD and MAD studies in healthy subjects (which were conducted in parallel to the early cohorts of the Phase 1b study) supported the escalation to 180 mg in Cohort 3.

In Study CP0514, the lowest pegcetacoplan dose with pharmacologic activity was 180 mg daily SC. Improved efficacy was observed with a daily SC dose of 270 mg. Specifically, all 6 subjects in Cohort 4 had a clinically meaningful improvements in hematologic parameters (e.g. Hb and LDH levels) with a SC dose of 270 mg/d in combination with eculizumab. Four subjects transitioned to pegcetacoplan monotherapy during the study, and of these, 3 required a further increase in dose to 360 mg/day (1 of these 3 subjects needed a further increase of the equivalent of 440 mg/day) to maintain their hematologic response.

Repeated dosing of pegcetacoplan in 20 subjects with PNH naive to treatment with a complement inhibitor was conducted in Study 204. In this setting, pegcetacoplan again demonstrated efficacy at a daily SC dose of 270 mg, as evidenced by improvements in Hb levels and reductions in LDH levels. Specifically, 17 subjects received pegcetacoplan at a daily SC dose of 270 mg for at least 364 days. Three of 20 subjects needed a dose adjustment from 270 mg/d to 360 mg/d during the study.

The cumulative data of Study 204, Study CP0514 (Cohort 4), and Phase 2a Study 202 suggested that most subjects (at least 22 of 30) had a clinically meaningful response with pegcetacoplan monotherapy at 270 mg/d dose. A few subjects (6 of 30) needed a 360 mg/d dosage or higher to sustain robust clinical response during long-term treatment of pegcetacoplan monotherapy. The exposure of pegcetacoplan in these subjects at 270 mg/day, as measured by their pegcetacoplan serum concentration, was lower when compared to that of the majority of other subjects on this same dose. With dose adjustment, both the exposure and clinical responses improved for these subjects.

To reduce the burden of daily dosing on subjects and to promote dosing compliance, the effectiveness of less frequent dosing regimens, such as twice-weekly dosing, was investigated. A twice-weekly dose of 1080 mg was selected as the dosing regimen for the registrational trials on the basis of preliminary PK modelling, which predicted a pegcetacoplan serum level for this regimen between those observed for the 270 mg and 360 mg daily dose regimens, potentially striking a balance between identifying a minimally effective dose and optimizing the potential clinical response for a broad PNH patient population. The pegcetacoplan serum concentration predicted for 1080 mg twice weekly SC dosing was confirmed in Study 101 in healthy subjects.

Population PK modelling based on pooled data from 10 clinical studies, including data up to Week 16 from Study APL2-302, confirmed that the pegcetacoplan exposure achieved in subjects with PNH at a dose of 1080 mg SC twice weekly is intermediate to those predicted for doses of 270 mg and 360 mg SC once daily.

In Study APL2-302, the pegcetacoplan dosing regimen was 1080 mg twice-weekly. Although dose escalation to a regimen of 1080 mg every 3 days was allowed, this change in dose frequency was implemented in only 1 subject through Week 16. Therefore, based on the results of Study APL2-302, a dose of regimen of 1080 mg twice-weekly has been determined to meet the clinical needs of PNH patients.

The exposure-response model for Hb provides support for the hypothesis that the Phase 3 dose regimen of 1080 mg twice weekly is an effective dose for Hb response. Steady-state pegcetacoplan serum concentrations are expected to reach 99% of the maximal predicted Hb response. The exposure-response model for LDH also provides support for the hypothesis that the Phase 3 dose regimen of 1080 mg twice weekly is an effective dose for LDH response. Steady-state pegcetacoplan serum concentrations are expected to reach 95% of the maximal predicted LDH response, regardless of prior treatment with eculizumab.

2.6.5.2. Main study

APL2-302 study: A phase 3, randomized, multicenter, open-label, active-comparator controlled study to evaluate the efficacy and safety of pegcetacoplan in patients with paroxysmal nocturnal hemoglobinuria (pnh)

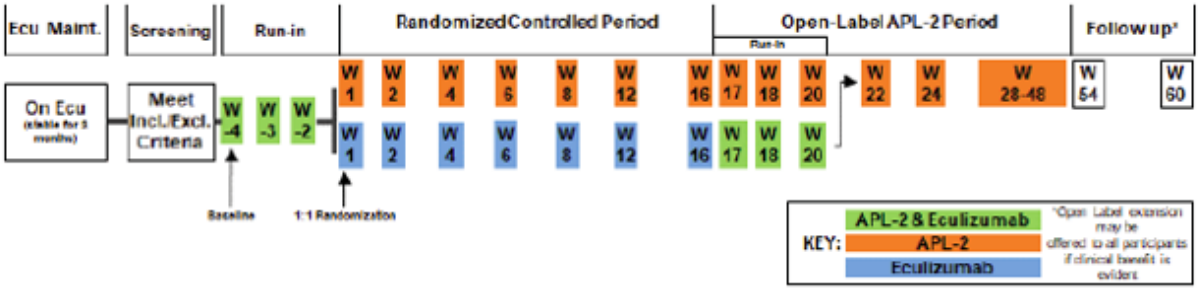
Methods

Study APL2-302 is considered the pivotal study to provide the evidence of efficacy and safety. This is a global, Phase 3, prospective, randomized, multicenter, open-label, active comparator controlled study. Its objective is to confirm treatment efficacy and safety of pegcetacoplan monotherapy for the treatment of PNH in subjects aged ≥18 years who were receiving eculizumab therapy but continued to have Hb levels <10.5 g/dL. Subjects were randomized to receive pegcetacoplan 1080 mg twice weekly or every 3 days if clinically indicated or their current dosage of eculizumab. This head-to-head comparator trial was designed to demonstrate superiority of pegcetacoplan to eculizumab monotherapy in subjects with PNH currently on treatment with eculizumab as measured by change in Hb level at Week 16. The 16-week RCP is completed; the 32-week open-label period is ongoing.

After completion of the randomized controlled period (RCP) (the end of Week 16), subjects continue into a 32-week open-label pegcetacoplan period in which all subjects receive twice-weekly doses of pegcetacoplan 1080 mg. Subjects who received eculizumab in the RCP received pegcetacoplan in addition to eculizumab for 4 weeks (Weeks 17 to 20). After completion of the 52-week treatment period (Week 48), subjects are offered entry into an open-label extension study. Subjects who do not enter the open-label extension study exit the study after 2 additional safety visits.

The planned length of participation in the study overall for each subject was a maximum of approximately 72 weeks, including an 8-week screening period, 52-week treatment period and, for those do not enter the open-label extension study, a 12-week follow-up period.

This report includes data through Week 16, which is the primary endpoint of this study.



Abbreviations: APL-2 = pegcetacoplan; Ecu = eculizumab; Excl. = exclusion; Incl. = inclusion; W = Week.

Figure 7: Study Design

Forty-four sites participated in this study across Australia, Belgium, Canada, France, Germany, Japan, Russia, South Korea, Spain, United Kingdom, and the United States of America.

Study Participants

At screening (unless otherwise specified), adult subjects were required to fulfill all of the following **inclusion criteria** to be eligible for participation in the study, notably

Primary diagnosis of PNH confirmed by high-sensitivity flow cytometry, on treatment with eculizumab. Dosage of eculizumab must have been stable for at least 3 months prior to the screening visit, Hb <10.5 g/dL at the screening visit, ARC >1.0× the upper limit of normal (ULN) at the screening visit, platelet count of >50,000/mm3 at the screening visit, and absolute neutrophil count >500/mm3 at the screening visit.

Treatments

Pegcetacoplan was provided as a sterile solution, 54 mg/mL, in acetate-buffered sorbitol in 20-cc stoppered glass vials and was required to be stored refrigerated at 2 to 8 °C.

Pegcetacoplan was administered as a 20-mL SC infusion.

Starting on Day –28 (Visit 2), subjects received twice-weekly SC doses of 1080 mg of pegcetacoplan in addition to their current dosage of eculizumab until Day 1. Subjects maintained their eculizumab dose and administration schedule as prescribed, regardless of study visit scheduling or the pegcetacoplan administration schedule.

Following completion of the run-in period, subjects were randomly assigned (1:1) to receive either 1080 mg of pegcetacoplan twice weekly or their current dosage of eculizumab. If a subject did not respond sufficiently to the planned dosage of 1080 mg twice weekly (for subjects receiving pegcetacoplan monotherapy, if LDH was >2 × ULN), the dosing regimen could be changed to 1080 mg every third day upon agreement with the sponsor.

Objectives

The primary objectives of this study were to establish the efficacy and safety of pegcetacoplan compared with those of eculizumab in subjects with PNH who continued to have Hb levels <10.5 g/dL despite treatment with eculizumab.

Outcomes/endpoints

Primary Efficacy Endpoint:

- Change from baseline (CFB) to Week 16, excluding data before the randomized controlled period (RCP), in Hb level

Key Secondary Efficacy Endpoints:

- Transfusion avoidance (Yes/No), defined as the proportion of subjects who do not require a transfusion during the study during the RCP
- CFB to Week 16, excluding data before the RCP, in absolute reticulocyte count (ARC)
- CFB to Week 16, excluding data before the RCP, in lactate dehydrogenase (LDH) level
- CFB to Week 16, excluding data before the RCP, in FACIT-Fatigue Scale score, Version 4

Secondary Efficacy Endpoints:

- Hb response in the absence of transfusions (Yes/No). Hb response of at least ≥1 g/dL in Hb from Baseline at Week 16, excluding data before the RCP.
- Reticulocyte normalization in the absence of transfusions (Yes/No). Reticulocyte normalization is defined as the ARC being below the upper limit of the normal range at Week 16
- Hb normalization in the absence of transfusions (Yes/No). Hemoglobin normalization is defined as the Hb level being above the lower limit of the normal range at Week 16
- CFB to Week 16, excluding data before the RCP, in indirect bilirubin level, in haptoglobin level
- CFB to Week 16, excluding data before the RCP, in Linear Analog Scale Assessment (LASA) scores, in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 Scale (QLQ-C30) scores
- Number of packed red blood cell (PRBC) units transfused during the RCP [>Day 1 to Week 16 and Week 4 to Week 16].

Sample size

Sample size of 64 randomly assigned subjects (32 in each group).

Randomisation and Blinding (masking)

Subjects who met all the eligibility criteria were eligible to enter the 4-week run-in period. Following completion of the run-in period, subjects were randomly assigned (1:1) using interactive response technology to receive either pegcetacoplan or eculizumab.

Treatment assignment was not blinded.

Statistical methods

A sample size of 64 randomly assigned subjects (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, Week 16 CFB in Hb level. This assumed a treatment difference between pegcetacoplan and eculizumab of 1 g/dL and a standard deviation for the CFB of 1.2 g/dL (effect size = 0.833). To account for loss of power due to discontinuations, the study attempted to randomize 70 subjects. It was anticipated that more than 70 subjects would need to enter the run-in period to achieve 70 randomly assigned subjects.

The primary analysis was carried out on the intent-to-treat as randomized population. The primary efficacy endpoint was the CFB in Hb level at Week 16 of the RCP. If a subject received a transfusion during the RCP or withdrew from the study, the Hb levels up to the transfusion or time of withdrawal were included. If a subject received a transfusion, the pretransfusion Hb value from the local laboratory was used; however, if it was not collected or missing, then the pretransfusion central laboratory Hb value was used.

The between-treatment-group comparison for the primary efficacy endpoint was performed using a mixed-effect model for repeated measures (MMRM) (Mallinckrodt et al. 2008).

The model included the treatment effect as fixed effect and will be adjusted on visits, stratification factors (number of PRBC transfusion prior inclusion / < 4; ≥4 and platelet count at screening / >100 000; ≥100 000), visit-by-treatment interaction and covariate baseline Hb level.

The difference between pegcetacoplan and eculizumab mean Hb changes from baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P value from the MMRM model.

Intercurrent events (ICE) that were considered in the analysis of the primary objective include transfusions, discontinuation of study treatment, and withdrawal from the study.

Supportive analyses of the primary efficacy endpoint included the following:

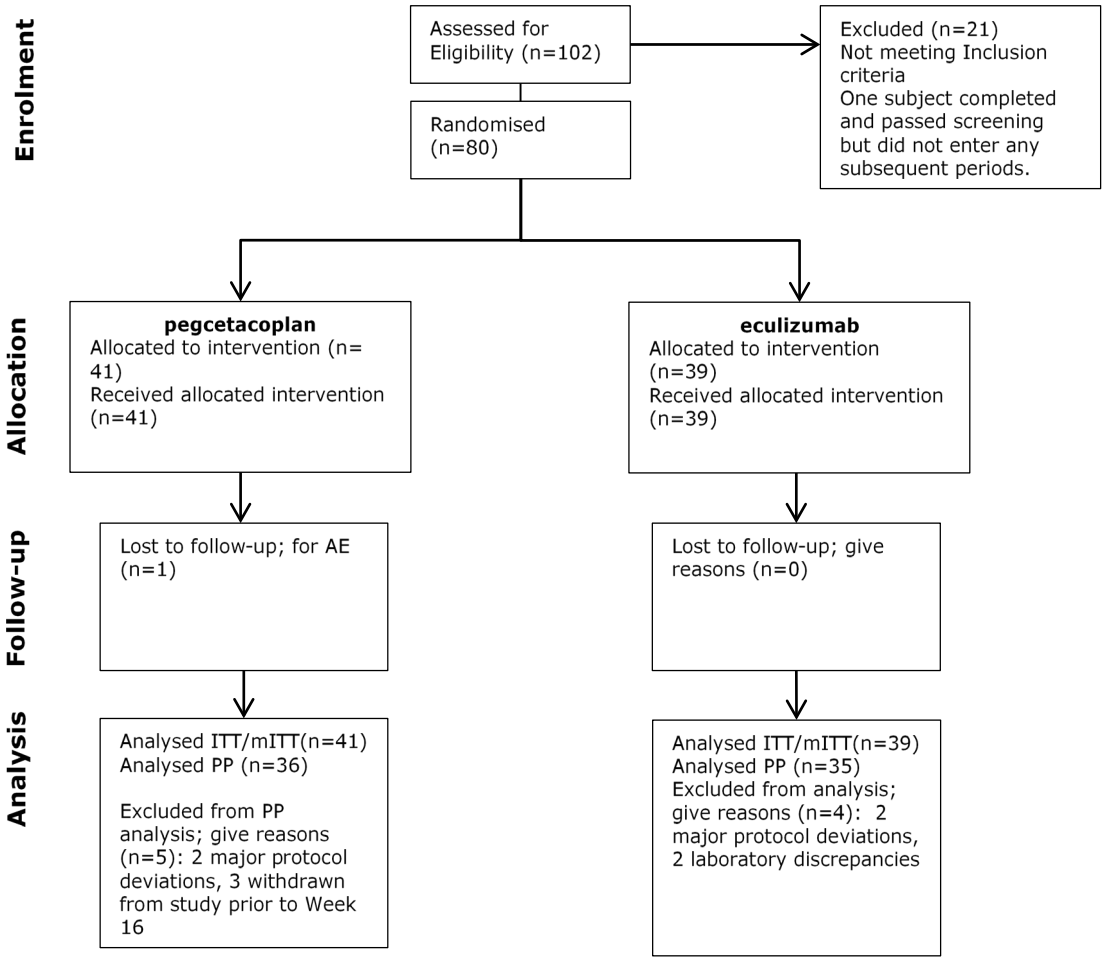
- An MMRM analysis using the PP set using data up to ICE.
- An MMRM analysis using the mITT set using all available data (uncensored for transfusion) after Week 4.
- An MMRM analysis using data uncensored for transfusion from the ITT set, regardless of whether the Hb measurement was following a transfusion.
- An MMRM analysis using the completers set using data up to ICE.

Key secondary endpoints were tested in a hierarchical manner after statistical significance was reached for the primary endpoint. Key secondary endpoints were tested first for non-inferiority and, if all were met, then superiority was tested sequentially for transfusion avoidance, ARC, LDH, and FACIT-Fatigue score using a closed-testing procedure at a significance level of 0.05.

For categorical secondary efficacy endpoints, the number and percentage of subjects meeting the following criteria was tabulated by treatment group at Week 16 and the superiority test was used to compare the 2 treatment groups: Hb response (≥1 g/dL increase from baseline in the absence of transfusion), Reticulocyte normalization (≤ULN), Hb normalization (≥ the lower limit of normal).

Results

- **Participant flow**



Recruitment

Forty-four sites participated in this study across Australia, Belgium, Canada, France, Germany, Japan, Russia, South Korea, Spain, United Kingdom, and the United States of America. One clinical site of was closed due to GCP noncompliance. Two subjects were enrolled at this site. GCP quality assurance audits were conducted at 14 clinical sites.

Conduct of the study

Table 8: Brief Summary of Protocol Amendment Changes Made

Protocol amendment	Effective date	Main changes made
Version 1	3 October 2017	This version was not used.
Version 2	22 November 2017	This version was not used.
Version 3	30 March 2018	Original protocol
Protocol Amendment 1 Version 1.0	13 August 2018	This version was not used.
Protocol Amendment 1 Version 2.0	21 August 2018	Allowed subjects to proceed to Visit 2 at any time (rather than waiting at least 2 weeks) after confirmation of study eligibility. Clarified the appropriate 6-hour postdose PK sample window: ±30 minutes End of trial was defined as follows: *The end of the trial is defined as when the last subject either completes their Week 48 visit and enrolls in the long-term safety extension (LTSE) study, or, should a subject elect not to enter the LTSE study, when the last subject completes their exit visit at Week 60.* Clarified that during the 4-week run-in period (Week -4 to Day -1), Visit 5 (Day 1), and through the course of the study, pegcetacoplan administration and study visits should be conducted and scheduled independently of each subject's regular eculizumab administration schedule. Inclusion Criterion #13: added to require that subjects have a BMI ≤40 in order to qualify for study entry. Inclusion Criterion #5: updated eligibility of ARC >1.0× ULN at screening visit (from previous requirement of >1.5× ULN). Lactate dehydrogenase isoenzymes and erythropoietin were added to the serum chemistry panel.

Protocol amendment	Effective date	Main changes made
Protocol Amendment 2 Version 1.0	13 December 2018	Screening window extended to up to 8 weeks (Week -12) Clarified that use of silica reagents in coagulation panels was to be avoided. Added emphasis that subjects should be instructed to take pegcetacoplan treatment as prescribed and should contact the investigator immediately for guidance in the event of any missed doses. Allowed administration of eculizumab at home. Clarified that there was no requirement for eculizumab to be administered on the day of a study visit. Clarified that subjects administer pegcetacoplan at the study site through the run-in period and on Day 1. After that, every effort should be made to ensure that the subject's pegcetacoplan dosing schedule aligned with study visit days. If not possible, dosing should occur according to the dosing schedule and not the visit schedule, as there was no requirement for subjects to administer pegcetacoplan at the study site. Noted that if a screening visit was more than 28 days before dosing, the hematology panel should be repeated.

Protocol amendment	Effective date	Main changes made
Protocol Amendment 3 Version 1.0	08 February 2019	This amendment re-arranged secondary endpoints into key secondary and secondary endpoints. The classification of "tertiary endpoints" was removed and former tertiary endpoints were reclassified as secondary endpoints. The duration of when the endpoint was being assessed was specified within some endpoint descriptions for clarity. Modified randomization stratification factors as follows: 1. Number of PRBC transfusions within the 12 months prior to Day -28 (<4; ≥4) 2. Platelet count at screening (<100,000; ≥100,000) The study diagram and descriptions of the study were modified to remove references to the wash-out period. Modified Inclusion Criterion #13: excluded subjects with Class 2 or greater obesity (subjects with a BMI ≥35.0 kg/m2)
Protocol Amendment 4 Version 1.0	16 August 2019	Clarified *S. pneumoniae* vaccination requirements Clarified that during the screening period (from up to Week -12 to Week -4), clinical laboratory tests (eg, hematology, coagulation, serum chemistry, flow cytometry, urinalysis) could be repeated with written approval from the sponsor (including the assigned medical monitor), with no requirement to designate the subject as a screen failure. Dose adjustment was updated to mandate dose escalation to 1080 mg every third day upon the first instance of LDH >2× ULN, rather than requiring LDH to be elevated on 2 consecutive occasions at least 1 week apart. Clarified subject transfusion history collection requirements.

Protocol amendment	Effective date	Main changes made
Administrative Clarification Memorandum	19 June 2018	Clarified the following: • The terminology that should be used to classify AE outcomes: *Clinical Data Interchange Standards Consortium (CDISC) standards* • The appropriate 6-hour postdose PK sample window: *±30 minutes* • The required duration between Visit 1 (screening) and Visit 2 (Day -28): *None, once screening requirements are satisfied*
Administrative Clarification Memorandum	09 July 2018	Clarified that during the 4-week run-in period (Week -4 to Day -1), Visit 5 (Day 1), and through the course of the study, pegcetacoplan administration and study visits should be conducted and scheduled independently of each subject's regular eculizumab administration schedule.
Administrative Clarification Memorandum	28 February 2019	Clarified that during the screening period (from up to Week -12 to Week -4), clinical laboratory tests (eg, hematology, coagulation, serum chemistry, flow cytometry, urinalysis) could be repeated with written approval from the sponsor (including the assigned Medical Monitor), with no requirement to designate the subject as a screen failure.
Administrative Clarification Memorandum	08 March 2019	Clarified subject transfusion history collection requirements. Specified that a subject's transfusion history from the previous 12 months should be collected at the Visit 1 Screening Visit. At Visit 2, transfusion history should be reviewed, and any transfusions received between Visit 1 and Visit 2 should be recorded.
Administrative Clarification Memorandum	12 August 2019	Clarified that subjects enrolling in the study were required to be vaccinated against *Streptococcus pneumoniae* unless there was documented evidence that a subject was a nonresponder.

Forty-four sites participated in this study across Australia, Belgium, Canada, France, Germany, Japan,

- **Baseline data**

Table 9: Demographic Characteristics by Treatment Group (ITT Set)

	Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)	Total (N = 80)
Age (years)	n	41	39	80
	Mean (SD)	50.2 (16.29)	47.3 (15.81)	48.8 (16.02)
≤65 years	n (%)	31 (75.6)	32 (82.1)	63 (78.8)
>65 years	n (%)	10 (24.4)	7 (17.9)	17 (21.3)
Sex				
Female	n (%)	27 (65.9)	22 (56.4)	49 (61.3)
Male	n (%)	14 (34.1)	17 (43.6)	31 (38.8)
Race				
Asian	n (%)	5 (12.2)	7 (17.9)	12 (15.0)
Black or African American	n (%)	2 (4.9)	0	2 (2.5)
White	n (%)	24 (58.5)	25 (64.1)	49 (61.3)
Other	n (%)	0	1 (2.6)	1 (1.3)
Not Reported	n (%)	10 (24.4)	6 (15.4)	16 (20.0)
Ethnicity				
Hispanic or Latino	n (%)	2 (4.9)	1 (2.6)	3 (3.8)
Not Hispanic or Latino	n (%)	29 (70.7)	32 (82.1)	61 (76.3)
Not Reported	n (%)	10 (24.4)	6 (15.4)	16 (20.0)
Region				
APAC	n (%)	6 (14.6)	12 (30.8)	18 (22.5)
EU	n (%)	25 (61.0)	19 (48.7)	44 (55.0)
NA	n (%)	10 (24.4)	8 (20.5)	18 (22.5)
Weight (kg)	n	41	39	80
	Mean (SD)	75.86 (18.765)	74.60 (16.615)	75.25 (17.649)
Height (cm)	n	41	39	80
	Mean (SD)	167.72 (10.270)	169.06 (8.718)	168.37 (9.509)
BMI (kg/m^2)	n	41	39	80

	Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)	Total (N = 80)
	Mean (SD)	26.731 (4.3259)	25.898 (4.2683)	26.325 (4.2911)
<18.5	n (%)	0	0	0
≥18.5 - <25	n (%)	18 (43.9)	17 (43.6)	35 (43.8)
≥25 - <30	n (%)	13 (31.7)	15 (38.5)	28 (35.0)
≥30 - <35	n (%)	8 (19.5)	7 (17.9)	15 (18.8)
≥35	n (%)	2 (4.9)	0	2 (2.5)

Abbreviation: APAC = Asia-Pacific, EU = Europe, NA = North America, SD = Standard Deviation.

Notes: Age (years) collected on CRF is used. Because some countries do not allow the collection of race and ethnicity, there is a category of not reported for race and ethnicity. Australia, Japan, Russia, and South Korea are included in APAC; Belgium, France, Germany, United Kingdom, and Spain are included in EU; United States of America and Canada are included in NA.

Table 10 : Baseline Characteristics by Treatment Group, ITT Set

Characteristics	Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)	Total (N = 80)
Time since diagnosis of PNH (years) to Day −28	N	41	39	80
	Mean (SD)	8.74 (7.364)	11.68 (9.582)	10.18 (8.592)
Duration (days) of treatment with eculizumab prior to Day −28	N	41	39	80
	Mean (SD)	1868.3 (1568.19)	1745.9 (1326.74)	1808.7 (1447.64)
Current eculizumab dosing level and dosing regimen				
Every 2 weeks intravenous 900 mg	n (%)	26 (63.4)	30 (76.9)	56 (70.0)
Intravenous 900 mg[a]	n (%)	1 (2.4)	0	1 (1.3)
Every 2 weeks intravenous 1200 mg	n (%)	12 (29.3)	9 (23.1)	21 (26.3)
Every 2 weeks intravenous 1500 mg	n (%)	2 (4.9)	0	2 (2.5)
Number of transfusions in the last 12 months prior to Day −28	N	41	39	80
	Mean (SD)	6.1 (7.26)	6.9 (7.72)	6.5 (7.45)
< 4	n (%)	20 (48.8)	16 (41.0)	36 (45.0)
≥ 4	n (%)	21 (51.2)	23 (59.0)	44 (55.0)
Platelet count at screening (/mm^3)	N	41	39	80
	Mean (SD)	166.6 (98.28)	146.9 (68.81)	157.0 (85.24)
<100,000 (count/mm^3)	n (%)	12 (29.3)	9 (23.1)	21 (26.3)
≥100,000 (count/mm^3)	n (%)	29 (70.7)	30 (76.9)	59 (73.8)
Time (days) since last transfusion prior to Day −28	N	31	28	59
	Mean (SD)	67.6 (68.01)	73.4 (96.27)	70.4 (81.95)
Hemoglobin level (g/dL)	N	41	39	80
	Mean (SD)	8.69 (1.075)	8.68 (0.886)	8.69 (0.982)
ARC (10^9 cells/mL)	N	41	39	80
	Mean (SD)	217.52 (74.964)	216.15 (69.136)	216.85 (71.729)
LDH level (U/L)	N	41	39	80
	Mean (SD)	257.48 (97.648)	308.64 (284.842)	282.42 (210.991)
Haptoglobin level (g/L)	N	41	39	80
	Mean (SD)	0.144 (0.1253)	0.125 (0.1163)	0.135 (0.1206)
Total bilirubin level (µmol/L)	N	41	39	80
	Mean (SD)	42.52 (31.465)	40.51 (26.639)	41.54 (29.045)

Characteristics	Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)	Total (N = 80)
Indirect bilirubin level (µmol/L)	N	41	39	80
	Mean (SD)	34.65 (28.492)	32.89 (22.967)	33.80 (25.798)
Total FACIT-Fatigue score	N	41	38	79
	Mean (SD)	32.16 (11.380)	31.55 (12.513)	31.87 (11.865)

[a]Dosed once every 11 days.

Notes: All baseline laboratory values except hemoglobin are the average of values recorded prior to dosing with pegcetacoplan at Day –28 using central Lab. The average baseline value for hemoglobin (Hb) includes local and central laboratory values assessed prior to first dose of pegcetacoplan at Day –28.

Baseline of FACIT-Fatigue score is the last available, nonmissing observation prior to first pegcetacoplan administration.

If the laboratory results were collected as <= or >= a numeric value, 0.0000000001 was subtracted or added, respectively, to the value.

Day –28 is the first date of pegcetacoplan during the run-in period for the study.

Table 11: Baseline Number of PRBC Transfusions Within the 12 Months Prior to Day –28

Number of transfusions in prior 12 months	Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)	Total (N = 80)
0	n (%)	10 (24.4)	10 (25.6)	20 (25.0)
1	n (%)	4 (9.8)	3 (7.7)	7 (8.8)
2	n (%)	3 (7.3)	3 (7.7)	6 (7.5)
3	n (%)	3 (7.3)	0	3 (3.8)
≥4	n (%)	21 (51.2)	23 (59.0)	44 (55)

Table 12: Medical History in ⩾10% of subjects (safety set)

Preferred term	Pegcetacoplan (N = 41) n (%)	Eculizumab (N = 39) n (%)	Total (N = 80) n (%)
Iron overload	9 (22.0)	12 (30.8)	21 (26.3)
Aplastic anemia	11 (26.8)	9 (23.1)	20 (25.0)
Hypertension	10 (24.4)	9 (23.1)	19 (23.8)
Fatigue	8 (19.5)	10 (25.6)	18 (22.5)
Anemia	9 (22.0)	7 (17.9)	16 (20.0)
Dyspnea	9 (22.0)	7 (17.9)	16 (20.0)
Cholecystectomy	8 (19.5)	5 (12.8)	13 (16.3)
Headache	6 (14.6)	3 (7.7)	9 (11.3)
Back pain	5 (12.2)	4 (10.3)	9 (11.3)
Osteoarthritis	4 (9.8)	5 (12.8)	9 (11.3)
Depression	5 (12.2)	4 (10.3)	9 (11.3)
Hemoglobinuria	5 (12.2)	3 (7.7)	8 (10.0)
Hemolysis	3 (7.3)	5 (12.8)	8 (10.0)
Asthenia	5 (12.2)	3 (7.7)	8 (10.0)
Insomnia	4 (9.8)	4 (10.3)	8 (10.0)

Table 13 : Thrombosis History by Treatment Group (Safety Set)

System organ class/ preferred term	Pegcetacoplan (N = 41) n (%)	Eculizumab (N = 39) n (%)	Total (N = 80) n (%)
Subjects with at least one type of Thrombosis	15 (36.6)	10 (25.6)	25 (31.3)
Vascular disorders	6 (14.6)	4 (10.3)	10 (12.5)
Deep vein thrombosis	6 (14.6)	1 (2.6)	7 (8.8)
Thrombosis	1 (2.4)	1 (2.6)	2 (2.5)
Thrombophlebitis	1 (2.4)	1 (2.6)	2 (2.5)
Arterial thrombosis	0	1 (2.6)	1 (1.3)
Axillary vein thrombosis	0	1 (2.6)	1 (1.3)
Jugular vein thrombosis	0	1 (2.6)	1 (1.3)
Subclavian vein thrombosis	0	1 (2.6)	1 (1.3)
Thrombophlebitis superficial	0	1 (2.6)	1 (1.3)
Venous thrombosis limb	0	1 (2.6)	1 (1.3)
Hepatobiliary disorders	5 (12.2)	5 (12.8)	10 (12.5)
Budd-Chiari syndrome	4 (9.8)	2 (5.1)	6 (7.5)
Hepatic vein thrombosis	1 (2.4)	3 (7.7)	4 (5.0)
Portal vein thrombosis	1 (2.4)	2 (5.1)	3 (3.8)
Nervous system disorders	1 (2.4)	2 (5.1)	3 (3.8)
Superior sagittal sinus thrombosis	0	2 (5.1)	2 (2.5)
Cerebral venous thrombosis	1 (2.4)	0	1 (1.3)
Transverse sinus thrombosis	0	1 (2.6)	1 (1.3)
Blood and lymphatic system disorders	0	3 (7.7)	3 (3.8)
Heparin-induced thrombocytopenia	0	2 (5.1)	2 (2.5)
Splenic thrombosis	0	1 (2.6)	1 (1.3)
Eye disorders	1 (2.4)	1 (2.6)	2 (2.5)
Retinal vein thrombosis	1 (2.4)	1 (2.6)	2 (2.5)
Respiratory, thoracic and mediastinal disorders	2 (4.9)	1 (2.6)	3 (3.8)
Pulmonary embolism	2 (4.9)	1 (2.6)	3 (3.8)
Gastrointestinal disorders	0	1 (2.6)	1 (1.3)
Mesenteric vein thrombosis	0	1 (2.6)	1 (1.3)
Renal and urinary disorders	1 (2.4)	0	1 (1.3)
Renal vein thrombosis	1 (2.4)	0	1 (1.3)

Notes: A subject will be included in more than one type of thrombosis if the subject experienced multiple types of thrombosis. Thrombosis history was coded to system organ class and Preferred Term using MedDRA 20.0 (Hierarchy)

Table 16. Numbers analysed

Analysis Population	Pegcetacoplan (N = 41) n (%)	Eculizumab (N = 39) n (%)	Total (N = 81) n (%)
Run-in set	NA	NA	80 (98.8)
Intent-to-treat set	41 (100)	39 (100)	80 (100)
Safety set	41 (100)	39 (100)	80 (100)
Modified ITT set (mITT)	41 (100)	39 (100)	80 (100)
Per-protocol set (PP)	36 (87.8)	35 (89.7)	71 (88.8)
Completer set	37 (90.2)	38 (97.4)	75 (93.8)
Pharmacokinetic set	41 (100)	39 (100)	80 (100)
Pharmacodynamic set	41 (100)	39 (100)	80 (100)

Abbreviation: NA = not applicable
Note: Subject 01002001 passed the screening period but did not enroll in any additional study periods.

Outcomes and estimation

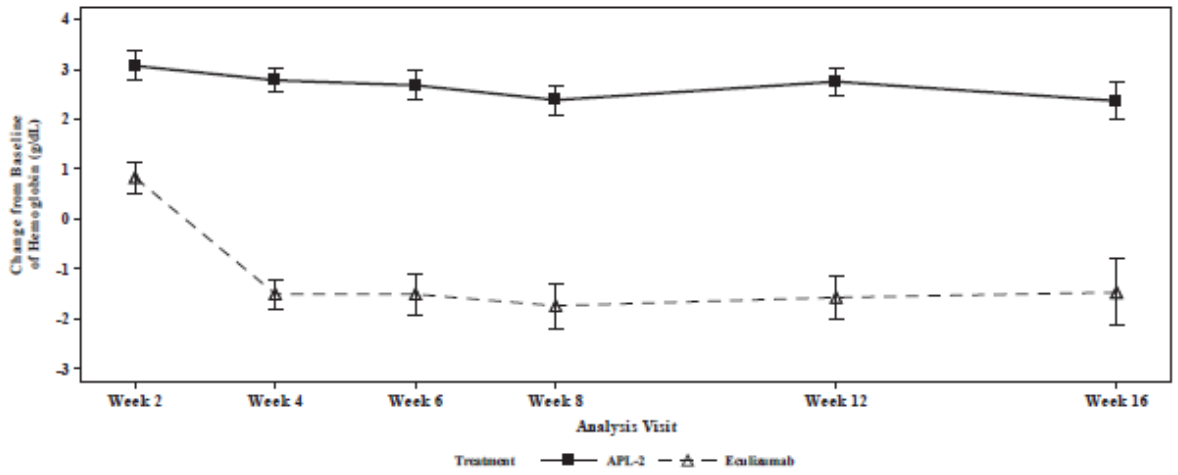
Primary endpoint

With the MMRM analysis, the least-square (LS) mean CFB in Hb at Week 16 in the pegcetacoplan and eculizumab groups was 2.37 g/dL and -1.47 g/dL, respectively (see the following table). The difference in LS mean CFB in Hb between the 2 groups of 3.84 g/dL was statistically significant (95% CI 2.33, 5.34; P<.0001) and higher than the pre-specified difference between pegcetacoplan and eculizumab of 1 g/dl. The primary endpoint has been reached. A large number of subjects received transfusions in eculizumab arm (n=33) compared to pegcetacoplan arm (n=5). These data reflect a superiority of pegcetacoplan compared to eculizumab in terms of efficacy of control of the disease.

Table 14: Primary Analysis: Change From Baseline in Hemoglobin During Randomized Controlled Period Using MMRM Model, Censored for Transfusion (ITT Set)

	Pegcetacoplan (N = 41) LS mean (SE) g/dL	Eculizumab (N = 39) LS mean (SE) g/dL	Difference (95% CI)	*P* value
Week 2	3.07 (0.289)	0.83 (0.306)	2.24 (1.45, 3.03)	<.0001[a]
Week 4	2.78 (0.249)	−1.50 (0.295)	4.28 (3.56, 5.00)	<.0001[a]
Week 6	2.68 (0.285)	−1.51 (0.411)	4.19 (3.23, 5.14)	<.0001[a]
Week 8	2.38 (0.303)	−1.74 (0.451)	4.12 (3.07, 5.18)	<.0001[a]
Week 12	2.75 (0.285)	−1.57 (0.422)	4.33 (3.34, 5.31)	<.0001[a]
Week 16	**2.37 (0.363)**	**−1.47 (0.666)**	**3.84 (2.33, 5.34)**	**<.0001[a]**

Abbreviations: ITT = intent-to-treat; LS = least-square.
[a] Significant at the 0.05 α level.
Notes: Baseline is the average of measurements recorded before taking the first dose of pegcetacoplan, which will include local and central laboratory values during the screening period. Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening. Data excluded from the absence of transfusions model. All values after intercurrent events were set to missing.



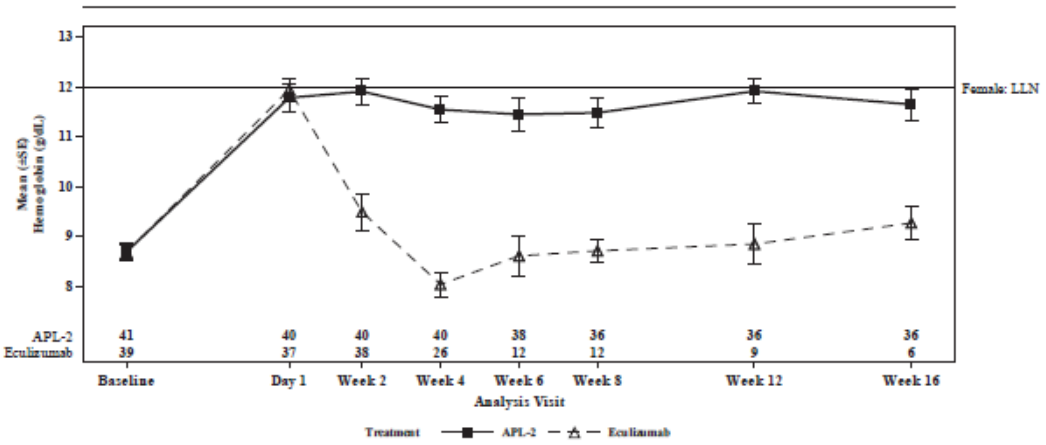
Abbreviation: LS mean = least squares mean
Baseline is the average of measurements recorded before taking the first dose of pegcetacoplan, which will include local and central laboratory values during the screening period.
For PRBC transfusion and withdrawal from the study: all measurements after the ICE events were set to missing.

Figure 8. LS Mean (± SE) Change From Baseline in Hemoglobin Using MMRM Model Over Time, Censored for Transfusion—Randomized Controlled Period (ITT Set)

Table 15: Descriptive Summary: Observed Values and Changes From Baseline in Hemoglobin During Randomized Controlled Period, Censored for Transfusion (ITT Set)

	Pegcetacoplan (N = 41)			Eculizumab (N = 39)		
Visit	n	Mean (SD) g/dL	CFB g/dL	n	Mean (SD) g/dL	CFB g/dL
Baseline	41	8.69 (1.075)	NA	39	8.68 (0.886)	NA
Week 2	40	11.91 (1.630)	3.18 (1.440)	38	9.49 (2.274)	0.76 (2.076)
Week 4	40	11.55 (1.619)	2.82 (1.376)	26	8.03 (1.264)	–0.82 (1.338)
Week 6	38	11.45 (2.008)	2.72 (1.650)	12	8.61 (1.391)	–0.32 (1.310)
Week 8	36	11.48 (1.863)	2.74 (1.701)	12	8.71 (0.763)	–0.37 (0.633)
Week 12	36	11.91 (1.538)	3.06 (1.513)	9	8.84 (1.228)	–0.39 (1.125)
Week 16	36	11.65 (1.885)	2.79 (2.030)	6	9.27 (0.841)	0.03 (0.437)

Abbreviations: CFB = change from baseline; ITT = intent-to-treat; NA = not applicable; RCP = randomized controlled period.



Baseline is the average of measurements recorded before taking the first dose of pegcetacoplan, which will include local and central laboratory values during the screening period.
For PRBC transfusion and withdrawal from the study: all measurements after the ICE events were be set to missing.
The normal range of central Hemoglobin (g/dL) for Female is [12, 16]
The normal range of central Hemoglobin (g/dL) for Male is [13.6, 18]
The normal range of local Hemoglobin (g/dL) is [11.2, 18]

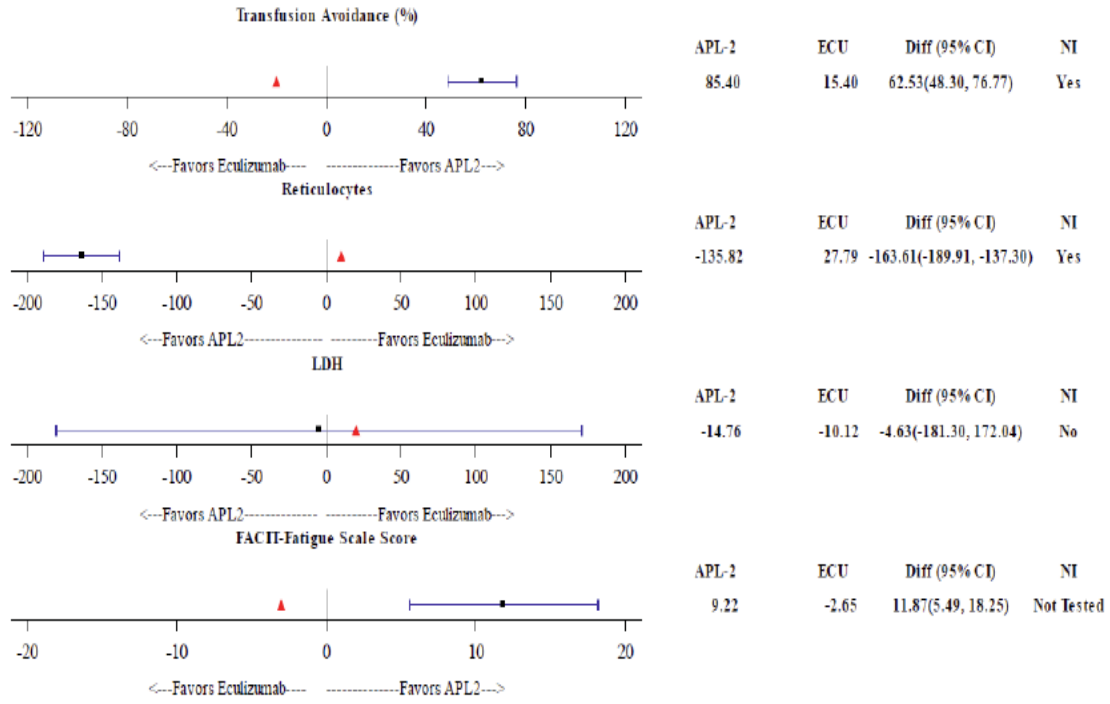
Figure 9: Mean (± SE) Plot of Hemoglobin Over Time, Censored for Transfusion—Randomized Controlled Period (ITT Set)

Key Secondary Endpoints

Key secondary endpoints were tested first for non-inferiority and, if all were met, then superiority was tested sequentially for transfusion avoidance, ARC, LDH, and FACIT-Fatigue score using a closed-testing procedure at a significance level of 0.05.

Transfusion Avoidance

The Figure below provides an overview of the results for the key secondary endpoints using a plot to display noninferiority margins and statistics.



Note: Red triangle represents NI margin, black square represents mean.
Abbreviations: LS mean = least squares mean
Transfusion avoidance (TA)—noninferiority (NI) test (2.5% level) using a NI margin of -20% for the difference between proportions.
Change from Baseline to Week 16 in ARC—NI test (2.5% level) using a NI margin of +10.
Change from Baseline to Week 16 in LDH—NI test (2.5% level) using a NI margin of +20.
Change from Baseline to Week 16 in FACIT-Fatigue score—NI test (2.5% level) using a NI margin of –3.

Figure 10: Plot of Noninferiority Margins And Statistics For Transfusion Avoidance, Reticulocyte Count, LDH, And FACIT-Fatigue Scores During Randomized Controlled Period (ITT Set)

Table 16: Summary for Number of Subjects With Transfusion Avoidance During Randomized Controlled Period (ITT Set)

Transfusions avoidance	Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Yes (no transfusion)	n (%)	35 (85.4)	6 (15.4)
No	n (%)	6 (14.6)	33 (84.6)
Received at least one transfusion[a]	n (%)	5 (83.3)	33 (100)
Withdrew from the study without having had a transfusion[a]	n (%)	1 (16.7)	0
Difference in percentage (pegcetacoplan - eculizumab)	Risk difference 95% CI Nominal *P* value	0.6253 0.4830, 0.7677 <.0001	

Abbreviations: ITT = intent-to-treat; RCP = randomized controlled period.
[a] Percentages are based on the number of subjects in No category for each column.
Transfusion avoidance is the proportion of subjects who did not require a transfusion during the RCP.
Subjects who experienced more than 1 transfusion during RCP are only counted once.
Subjects who did not have a transfusion but withdrew before Week 16 were considered as having a transfusion in the analysis of transfusion avoidance.
The 95% CI for difference in percentage between treatments is constructed using the stratified (Miettinen-Nurminen) method.

Pegcetacoplan met non-inferiority to eculizumab on transfusion avoidance, with 85.4% of pegcetacoplan subjects and 15.4% of eculizumab subjects achieving transfusion avoidance (nominal P value <.0001).

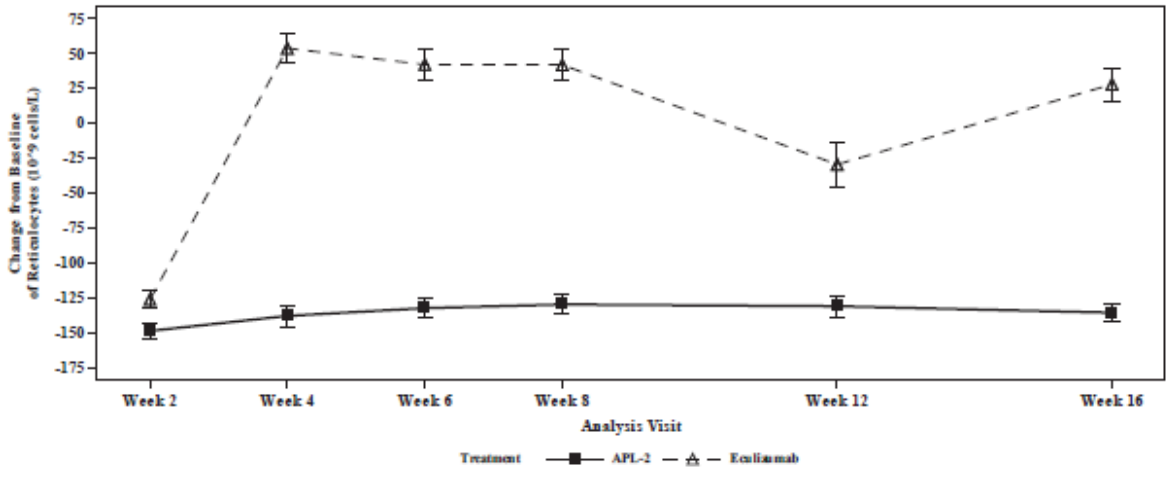
This result is significantly clinically relevant. The proportion of subjects who were transfusion avoidant was similar in the pegcetacoplan group, regardless of baseline PRBC transfusion strata or baseline platelet strata, but not in the eculizumab group.

Absolute Reticulocyte Count

Table 17: MMRM Model: Changes From Baseline in Reticulocyte Count During Randomized Controlled Period, Censored for Transfusion (ITT Set)

	Pegcetacoplan (N = 41) LS mean (SE) (10^9 cells/L)	Eculizumab (N = 39) LS mean (SE) (10^9 cells/L)	Difference (95% CI) in LS mean (vs eculizumab) (10^9 cells/L)	Nominal *P* value
Week 2	−148.88 (5.945)	−126.42 (6.349)	−22.46 (−38.72, −6.20)	.0075
Week 4	−138.11 (7.838)	53.64 (10.068)	−191.76 (−216.51, −167.0)	<.0001
Week 6	−132.54 (7.029)	41.86 (10.686)	−174.40 (−199.25, −149.55)	<.0001
Week 8	−129.91 (7.083)	41.71 (11.059)	−171.62 (−197.20, −146.03)	<.0001
Week 12	−131.17 (7.680)	−29.63 (15.851)	−101.54 (−136.51, −66.57)	<.0001
Week 16	−135.82 (6.543)	27.79 (11.859)	−163.61 (−189.91, −137.30)	<.0001

Abbreviations: ITT = intent-to-treat; LS = least-square; n = number of subjects with available data; RCP = randomized controlled period.
Notes: Baseline is the average of available measurements recorded from central laboratory before taking the first dose of pegcetacoplan.
Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening.



Abbreviations: ITT = intent-to-treat; LS = least-square; MMRM = mixed model repeated measures.
Note: Baseline is the average of available measurements records from central labs prior to taking the first dose of pegcetacoplan. For PRBC transfusion and withdrawal from the study: all measurements after the ICE events were set to missing.

Figure 11: LS Mean (± SE) Change From Baseline in Absolute Reticulocyte Count Using MMRM Model Over Time, Censored for Transfusion—Randomized Controlled Period (ITT Set)

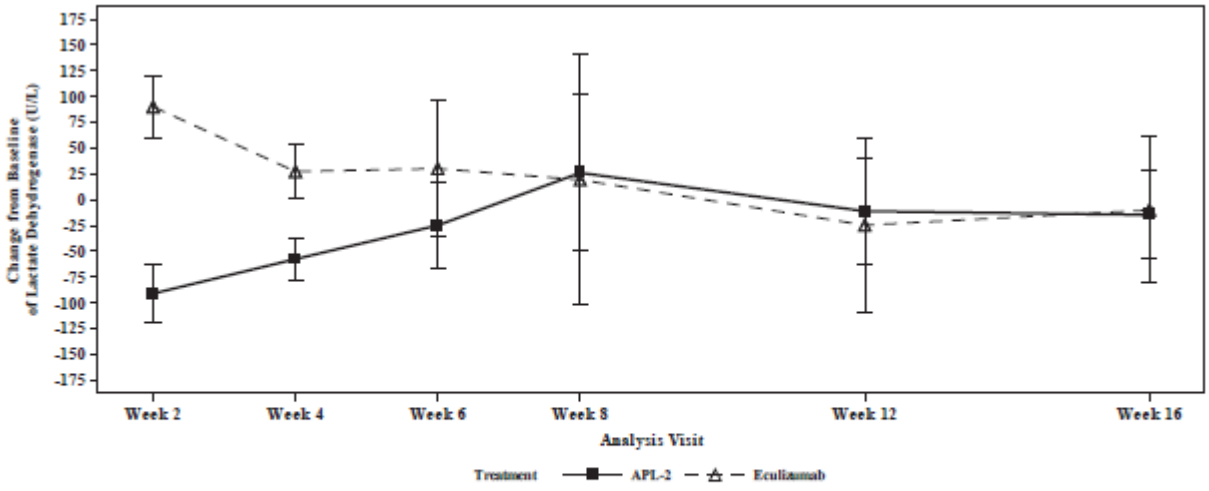
Pegcetacoplan was also non-inferior to eculizumab for CFB in ARC, a marker of hematopoietic bone marrow compensatory activity in the setting of anemia and/or hemolysis, with an LS mean difference of –163.6 × 109 cells/L (nominal P value <.0001).

Lactate Dehydrogenase (LDH)

Table 18: MMRM Model: Change From Baseline in LDH Level During Randomized Controlled Period, Censored for Transfusion (ITT Set)

Visit	Pegcetacoplan (N = 41) LS mean (SE) U/L	Eculizumab (N = 39) LS mean (SE) U/L	Difference (95% CI) in LS mean (vs eculizumab) U/L	Nominal *P* value
Week 2	–90.99 (27.734)	90.09 (29.524)	–181.08 (–257.68, –104.47)	<.0001
Week 4	–57.57 (20.188)	27.28 (26.876)	–84.85 (–148.47, –21.23)	.0107
Week 6	–24.83 (41.925)	30.12 (66.338)	–54.94 (–210.01, 100.12)	.4807
Week 8	26.05 (75.861)	19.28 (121.259)	6.77 (–290.68, 304.23)	.9625
Week 12	–11.11 (51.257)	–24.68 (83.745)	13.57 (–190.18, 217.32)	.8905
Week 16	–14.76 (42.708)	–10.12 (71.025)	–4.63 (–181.30, 172.04)	.9557

Abbreviation: LS = least-square.
Note: Baseline is the average of available measurements recorded from central laboratory prior to taking the first dose of investigational product pegcetacoplan.
Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening.
Data excluded from the model: All values after intercurrent events were set to missing.



Note: LS mean = least squares mean
Baseline is the average of available measurements records from central labs prior to taking the first dose of pegcetacoplan.
For PRBC transfusion and withdrawal from the study: all measurements after the ICE events were set to missing.

Figure 12: LS Mean (± SE) Change From Baseline in Lactate Dehydrogenase Level Using MMRM Model Over Time, Censored for Transfusion—Randomized Controlled Period (ITT Set)

LDH did not meet non-inferiority by the prespecified analysis. However, a greater percentage of subjects on pegcetacoplan achieved LDH normalization, as compared with eculizumab (71% vs 15%, respectively).

FACIT-Fatigue Score

Table 19: MMRM Model: Change From Baseline in FACIT-Fatigue Score During Randomized Controlled Period, Censored for Transfusion (ITT Set)

Visit	Pegcetacoplan (N = 41) LS mean (SE)	Eculizumab (N = 39) LS mean (SE)	Difference (95% CI) in LS mean (vs eculizumab)	Nominal *P* value
Week 2	10.79 (1.257)	0.45 (1.363)	10.34 (6.90, 13.78)	<.0001
Week 4	8.69 (1.526)	−4.41 (1.946)	13.10 (8.35, 17.84)	<.0001
Week 6	7.59 (1.600)	−5.37 (2.258)	12.95 (7.60, 18.31)	<.0001
Week 8	10.01 (1.438)	−3.49 (2.065)	13.50 (8.67, 18.33)	<.0001
Week 12	10.02 (1.328)	−3.71 (2.256)	13.74 (8.67, 18.80)	<.0001
Week 16	9.22 (1.607)	−2.65 (2.821)	11.87 (5.49, 18.25)	.0005

Abbreviations: FACIT = Functional Assessment of Chronic Illness Therapy; ITT = intent-to-treat; LS = least-square; MMRM = mixed-effect model for repeated measures.
Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan.
Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening.
Data excluded from the model: All values after intercurrent events were set to missing.

Noninferiority for the FACIT-Fatigue score was not assessed because of the prespecified hierarchical testing. Of note, a higher numerical improvements were seen in FACIT-Fatigue score in the pegcetacoplan group as compared with the eculizumab group with a difference of 11.87 points (95% CI 5.49, 18.25; nominal P value .0005).

Others Secondary endpoints

Hemoglobin Response

Table 20: Number and Percentage of Subjects With Hemoglobin Response at Week 16, Censored for Transfusion (ITT Set)

	Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Hemoglobin response			
Yes	n (%)	31 (75.6)	0
No	n (%)	10 (24.4)	39 (100.0)
Difference in percentage (pegcetacoplan vs eculizumab)	Difference	0.6745	
	95% CI	0.5452, 0.8039	

Abbreviation: ITT = intent-to-treat.
Hemoglobin response is an increase of at least ≥1 g/dL in hemoglobin from Baseline at Week 16, excluding data before the RCP.

Subjects who received a transfusion between Day 1 and Week 16 or withdraw without providing efficacy data at Week 16 were classified as nonresponders.
95% CI for difference in percentage is constructed using the stratified Miettinen-Nurminen method.

Reticulocyte Normalization

Table 21: Number and Percentage of Subjects With Reticulocyte Normalization at Week 16, Censored for Transfusion (ITT Set)

	Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Reticulocyte normalization censored for transfusion			
Yes	n (%)	32 (78.0)	1 (2.6)
No	n (%)	9 (22.0)	38 (97.4)
Difference in percentage (pegcetacoplan vs eculizumab)	Difference 95% CI	0.6639 0.5309, 0.7968	
Odds ratio (pegcetacoplan vs eculizumab)	OR 95% CI	135.5938 15.1916, 1210.2532	

Abbreviations: ITT = intent-to-treat; OR = odds ratio.
Reticulocyte normalization is a reticulocyte level below the upper limit of the gender-specific normal range at Week 16.
Subjects who received a transfusion between Day 1 and Week 16 or withdraw without providing efficacy data at Week 16 will be classified as nonresponders.
95% CI for difference in percentage is constructed using the stratified Miettinen-Nurminen method.
Both *P* value and 95% CI for Odds Ratio are obtained using the stratified Cochran-Mantel-Haenszel χ-square test.

Hemoglobin Normalization

Table 22: Number and Percentage of Subjects With Hemoglobin Normalization at Week 16, Censored for Transfusion (ITT Set)

	Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Hemoglobin normalization			
Yes	n (%)	14 (34.1)	0
No	n (%)	27 (65.9)	39 (100.0)
Difference in percentage (pegcetacoplan vs eculizumab)	Difference	0.3043	
	95% CI	0.1493, 0.4593	

Abbreviation: ITT = intent-to-treat.
Hemoglobin normalization is a hemoglobin level at or above the lower limit of the gender-specific normal range at Week 16.
Subjects who received a transfusion between Day 1 and Week 16 or withdrew without providing efficacy data at Week 16 are classified as nonnormalization.
95% CI for difference in percentage is constructed using the stratified Miettinen-Nurminen method.
Both *P* value and 95% CI for Odds Ratio are obtained using the stratified Cochran-Mantel Haenszel chi-square test.

Indirect Bilirubin

Table 23: MMRM Model: Change From Baseline in Indirect Bilirubin Level During Randomized Controlled Period, Censored for Transfusion (ITT Set)

Visit	Pegcetacoplan (N = 41) LS mean (SE) µmol/L	Eculizumab (N = 39) LS mean (SE) µmol/L	Difference (95% CI) µmol/L
Week 2	−21.94 (1.966)	0.95 (2.081)	−22.89 (−28.29, −17.49)
Week 4	−20.76 (1.615)	1.38 (1.944)	−22.14 (−26.86, −17.43)
Week 6	−18.31 (2.487)	6.96 (3.520)	−25.26 (−33.71, −16.82)
Week 8	−16.91 (2.558)	3.69 (3.928)	−20.60 (−30.00, −11.19)
Week 12	−18.64 (2.182)	−2.64 (3.575)	−16.00 (−24.34, −7.65)
Week 16	−17.78 (2.727)	4.15 (4.477)	−21.93 (−32.49, −11.36)

Abbreviations: ITT = intent-to-treat; LS = least square; MMRM = mixed model for repeated measures.

Notes: Baseline is the average of available measurements recorded from central laboratory prior to taking the first dose of investigational product pegcetacoplan.
Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening.
Data excluded from the model: All values after intercurrent events were set to missing.

Haptoglobin

Table 24: MMRM Model: Change From Baseline in Haptoglobin Level During Randomized Controlled Period, Censored for Transfusion (ITT Set)

Visit	Pegcetacoplan (N = 41) LS mean (SE) g/L	Eculizumab (N = 39) LS mean (SE) g/L	Difference (95% CI) in LS mean (vs eculizumab) g/L
Week 4	0.04 (0.032)	0.01 (0.043)	0.04 (−0.06, 0.14)
Week 8	−0.03 (0.033)	0.05 (0.054)	−0.07 (−0.19, 0.05)
Week 12	−0.02 (0.033)	0.10 (0.060)	−0.12 (−0.25, 0.01)
Week 16	−0.02 (0.033)	0.12 (0.063)	−0.14 (−0.28, −0.01)

Abbreviations: ITT = intent-to-treat; LS = least square; MMRM = mixed model for repeated measures.

Notes: Baseline is the average of available measurements recorded from central laboratory before taking the first dose of pegcetacoplan.
Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening.
Compound Symmetry was used as a covariance matrix.
Data excluded from the model: All values after intercurrent events were set to missing.

LASA Scores

Table 25: MMRM Model: Change From Baseline in LASA Scores During Randomized Controlled Period, Censored for Transfusion (ITT Set)

Visit	Pegcetacoplan (N = 41) LS mean (SE)	Eculizumab (N = 39) LS mean (SE)	Difference (95% CI) in LS mean (vs eculizumab)
Week 2	56.90 (8.653)	–0.94 (9.272)	57.84 (34.05, 81.63)
Week 4	54.57 (9.664)	–42.69 (12.267)	97.26 (67.29, 127.23)
Week 6	45.53 (9.997)	–49.53 (14.578)	95.06 (60.79, 129.33)
Week 8	52.24 (9.344)	–49.22 (15.515)	101.46 (66.39, 136.53)
Week 12	57.76 (10.394)	–26.29 (18.127)	84.05 (43.12, 124.98)
Week 16	49.38 (10.189)	–9.72 (18.988)	59.10 (16.88, 101.32)

Abbreviations: ITT = intent-to-treat; LS = least square; MMRM = mixed model for repeated measures.

Notes: Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan.
Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening.
Data excluded from the model: All values after intercurrent events were set to missing.

QLQ-C30 Scores

Table 26: MMRM Model: Change From Baseline to Week 16 in QLQ-C30 Scores During Randomized Controlled Period (ITT Set) by Parameter, Censored for Transfusion

	Pegcetacoplan N = 41 LS mean (SE)	Eculizumab N = 39 LS mean (SE)	Difference (95% CI)
Global Health Status/QoL	15.91 (3.635)	–2.71 (8.515)	18.62 (0.12, 37.13)
Functional scales			
Physical functioning	16.92 (2.081)	4.06 (3.605)	12.86 (4.86, 20.86)
Role functioning	15.39 (3.930)	–9.04 (6.954)	24.43 (8.84, 40.01)
Emotional functioning	7.98 (3.366)	3.86 (7.237)	4.11 (–11.58, 19.80)

	Pegcetacoplan N = 41 LS mean (SE)	Eculizumab N = 39 LS mean (SE)	Difference (95% CI)
Cognitive functioning	5.76 (3.258)	–3.80 (6.420)	9.56 (–4.52, 23.64)
Social functioning	15.08 (2.946)	3.82 (6.349)	11.27 (–2.38, 24.92)
Symptom Scales			
Fatigue	–22.93 (3.321)	–2.18 (6.644)	–20.74 (–35.29, –6.19)
Nausea and vomiting	–0.34 (1.632)	–0.33 (3.876)	–0.01 (–8.38, 8.35)
Pain	–0.74 (4.323)	2.01 (7.841)	–2.76 (–20.36, 14.85)
Dyspnoea	–20.12 (3.488)	–5.55 (7.019)	–14.57 (–29.90, 0.76)
Insomnia	–9.18 (3.955)	–9.50 (7.090)	0.32 (–15.67, 16.30)
Appetite loss	–3.76 (3.357)	4.19 (7.009)	–7.95 (–23.23, 7.33)
Constipation	2.98 (3.248)	1.19 (8.129)	1.79 (–15.70, 19.29)
Diarrhoea	0.31 (3.711)	1.68 (8.204)	–1.38 (–19.28, 16.52)
Financial difficulties	–6.82 (3.853)	0.58 (6.297)	–7.40 (–21.76, 6.95)

Abbreviations: ITT = intent-to-treat; LS = least square; MMRM = mixed model for repeated measures; QLQ-C30 = EORTC Quality of Life Questionnaire—Core 30 Scale; QoL = quality of life.
Notes: Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan.
Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening.
Data excluded from the model: All values after intercurrent events were set to missing.

Number of PRBC Units Transfused

Number of PRBC units transfused during the RCP (>Day 1 to Week 16 and Week 4 to Week 16) was assessed as a secondary endpoint. Subjects in the pegcetacoplan group required fewer units of PRBCs to be transfused (Table 48). This table includes Subject 01010003, who discontinued before receiving a transfusion.

The mean number of PRBC units required in the pegcetacoplan group was 0.6 and in the eculizumab group was 5.1 (95% CI: 2.0, 4.0).

Results for the mITT set (Week 4 to Week 16) were identical to the ITT set.

Table 30: Number of PRBC Units Transfused During Randomized Controlled Period (ITT Set)

Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Total units	26	198
Mean (SD)	0.6 (2.03)	5.1 (5.60)
Median	0.0	3.0
Min, Max	0, 11	0, 27
95% CI	2.0, 4.0	NA

Abbreviations: ITT = intent-to-treat; max = maximum; min = minimum; NA = not applicable; PRBC = packed red blood cell.
Wilcoxon rank-sum test *P* value for the comparison between treatments is based on median using stratified nonparametric analysis. The 95% CI is constructed using Hodges-Lehmann Estimation of Location Shift.
Note: Subjects who withdraw during the randomized controlled period before Week 16 will have their number of units of PRBC estimated from the duration they were in the study (ie, number per week × duration of endpoint). Hence the analysis of this endpoint will equate to an analysis of the frequency of transfusions.
APL-302-01010003 discontinued before transfusion hence the units of transfusion are 0.

- **Ancillary analyses**

Table 27: Supportive Analysis 1: Change From Baseline in Hemoglobin During Randomized Controlled Period Using MMRM-Uncensored for Transfusions (ITT Set)

	Pegcetacoplan (N = 41) LS mean (SE) g/dL	Eculizumab (N = 39) LS mean (SE) g/dL	Difference (95% CI)	*P* value
Week 2	3.18 (0.288)	0.84 (0.300)	2.34 (1.54, 3.14)	<.0001 [a]
Week 4	2.87 (0.228)	–0.52 (0.239)	3.39 (2.77, 4.02)	<.0001 [a]
Week 6	2.90 (0.212)	0.04 (0.226)	2.86 (2.28, 3.44)	<.0001 [a]
Week 8	2.61 (0.230)	–0.09 (0.239)	2.70 (2.07, 3.33)	<.0001 [a]
Week 12	2.94 (0.218)	–0.26 (0.228)	3.20 (2.61, 3.79)	<.0001 [a]
Week 16	2.66 (0.253)	–0.03 (0.261)	2.69 (1.99, 3.38)	<.0001 [a]

Abbreviation: LS = least-square.
[a] Significant at the 0.05 α level.
Notes: Baseline is the average of measurements recorded before taking the first dose of pegcetacoplan, which will include local and central laboratory values during the screening period.
Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where Strata is the combination of stratification factors number of transfusions and platelet count at screening.
Source: Table 14.2.1.3.1.

Table 28: Supportive Analysis 2, 3, and 4: Change From Baseline in Hemoglobin During Randomized Controlled Period Using MMRM Model (ITT, mITT, PP, and Completers Sets), Censored for Transfusion

	Pegcetacoplan N = 41 LS mean (SE) g/dL	Eculizumab N = 39 LS mean (SE) g/dL	Difference (95% CI) in LS mean (vs eculizumab) g/dL	*P* value
Week 16 ITT set	2.37 (0.363)	–1.47 (0.666)	3.84 (2.33-5.34)	<.0001[a]
Week 16 mITT set	2.57 (0.356)	–0.26 (0.689)	2.83 (1.33-4.33)	.0004[a]
Week 16 PP set	2.94 (0.287)	–1.31 (0.487)	4.25 (3.17-5.34)	<.0001[a]
Week 16 completers set	2.63 (0.344)	–1.48 (0.629)	4.11 (2.70-5.52)	<.0001[a]

Abbreviations: Diff = difference; ITT = intent-to-treat; LS = Least-square; mITT = modified intent-to-treat; MMRM = mixed-effect model for repeated measures; PP = per-protocol.

[a] Significant at the 0.05 α level.

Notes: Baseline is the average of measurements recorded before taking the first dose of pegcetacoplan, which will include local and central laboratory values during the screening period. Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening. Data excluded from the model: all values after intercurrent events were set to missing.

Source: Table 14.2.1.1.2, Table 14.2.1.3.2, Table 14.2.1.3.3, Table 14.2.1.3.4.

Table 33: Primary Analysis: Change From Baseline in Hemoglobin (g/dL) During Randomized Controlled Period Using MMRM Model by PRBC Transfusion, Censored for Transfusion (ITT Set)

	Pegcetacoplan LS mean (SE) g/dL	Eculizumab LS mean (SE) g/dL	Difference (95% CI) g/dL	*P* value
Number of PRBC transfusions <4				
n	20	16	NA	NA
Week 16	2.97 (0.364)	–0.01 (0.493)	2.98 (1.73, 4.23)	<.0001[a]
Number of PRBC transfusions ≥4				
	Pegcetacoplan Group LS mean (SE)	**Eculizumab Group LS mean (SE)**		
n	21	23	NA	NA
Week 16	2.11 (0.598)	–4.02 (2.395)	6.13 (0.79, 11.48)	.0278[a]

Abbreviations: ITT = intent-to-treat; LS = least square; NA = not applicable; PRBC = packed red blood cells.

[a] significant at the 0.05 α level.

Notes: Baseline is the average of measurements recorded before taking the first dose of pegcetacoplan, which will include local and central laboratory values during the screening period.

Model includes treatment + baseline value + analysis visit + analysis visit × treatment.

Data excluded from the model: All values after intercurrent events were set to missing.

Source: Table 14.2.1.1.4.

Table 29 Primary Analysis: Change From Baseline in Hemoglobin During Randomized Controlled Period Using MMRM Model by Platelet, Censored for Transfusion (ITT Set)

	Pegcetacoplan LS mean (SE) g/dL	Eculizumab LS mean (SE) g/dL	Difference (95% CI) g/dL	*P* value
Number of platelets <100,000/mm³				
n	12	9	NA	NA
Week 12	3.23 (0.673)	−1.84 (1.088)	5.08 (2.39, 7.77)	0.0007[a]
Number of platelets ≥100,000/mm³				
n	29	30	NA	NA
Week 16	2.18 (0.400)	−0.92 (0.743)	3.10 (1.37, 4.82)	0.0009[a]

Abbreviation: ITT = intent-to-treat; LS = least square; MMRM = mixed model for repeated measures; NA = not applicable.
Notes: Baseline is the average of measurements recorded before taking the first dose of pegcetacoplan, which will include local and central laboratory values during the screening period.
Model includes treatment + baseline value + analysis visit + analysis visit × treatment.
Data excluded from the model: All values after intercurrent events were set to missing.
Week 12 data are presented as there were no subjects in <100,000/mm³ stratum of the eculizumab group who did not receive transfusions by Week 16
[a] Significant at the 0.05 α level.
Source: Table 14.2.1.1.5.

Table 35: Primary Analysis: Change From Baseline in Hemoglobin During Randomized Controlled Period Using MMRM Model (ITT Set), Censored and Uncensored for Transfusion

	Censored for transfusion		Uncensored for transfusion	
	Pegcetacoplan (N = 41) g/dL	Eculizumab (N = 39) g/dL	Pegcetacoplan (N = 41) g/dL	Eculizumab (N = 39) g/dL
Week 2				
LS mean (SE)	3.07 (0.289)	0.83 (0.306)	3.18 (0.288)	0.84 (0.300)
95% CI of LS mean	(2.49, 3.64)	(0.22, 1.44)	(2.60, 3.75)	(0.24, 1.44)
Difference (95% CI) in LS mean (vs eculizumab)	2.24 (1.45, 3.03)	NA	2.34 (1.54, 3.14)	NA
Two-sided *P* value (vs eculizumab)	<.0001[a]	NA	<.0001[a]	NA
Week 4				
LS mean (SE)	2.78 (0.249)	−1.50 (0.295)	2.87 (0.228)	−0.52 (0.239)
95% CI of LS mean	(2.28, 3.28)	(−2.09, −0.91)	(2.42, 3.33)	(−1.00, −0.04)

	Censored for transfusion		Uncensored for transfusion	
Difference (95% CI) in LS mean (vs eculizumab)	4.28 (3.56, 5.00)	NA	3.38 (2.76, 4.01)	NA
Two-sided *P* value (vs eculizumab)	<.0001[a]	NA	<.0001[a]	NA
Week 6				
LS mean (SE)	2.68 (0.285)	–1.51 (0.411)	2.90 (0.212)	0.04 (0.226)
95% CI of LS mean	(2.10, 3.25)	(–2.33, –0.69)	(2.48, 3.33)	(–0.41, 0.49)
Diff (95% CI) in LS mean (vs eculizumab)	4.19 (3.23, 5.14)	NA	2.86 (2.28, 3.44)	NA
Two-sided *P* value (vs eculizumab)	<.0001[a]	NA	<.0001[a]	NA
Week 8				
LS mean (SE)	2.38 (0.303)	–1.74 (0.451)	2.61 (0.230)	–0.09 (0.239)
95% CI of LS mean	(1.77, 3.00)	(-2.65, -0.83)	(2.15, 3.07)	(–0.57, 0.38)
Diff (95% CI) in LS mean (vs eculizumab)	4.12 (3.07, 5.18)	NA	2.70 (2.07, 3.33)	NA
Two-sided *P* value (vs eculizumab)	<.0001[a]	NA	<.0001[a]	NA
Week 12				
LS mean (SE)	2.75 (0.285)	–1.57 (0.422)	2.94 (0.218)	–0.26 (0.228)
95% CI of LS mean	(2.18, 3.33)	(-2.42, -0.73)	(2.50, 3.37)	(–0.72, 0.19)
Diff (95% CI) in LS mean (vs eculizumab)	4.33 (3.34, 5.31)	NA	3.20 (2.60, 3.79)	NA
Two-sided *P* value (vs eculizumab)	<.0001[a]	NA	<.0001[a]	NA
Week 16				
LS mean (SE)	2.37 (0.363)	–1.47 (0.666)	2.66 (0.253)	–0.03 (0.261)
95% CI of LS mean	(1.63, 3.10)	(–2.81, –0.13)	(2.16, 3.16)	(–0.55, 0.49)
Diff (95% CI) in LS mean (vs eculizumab)	3.84 (2.33, 5.34)	NA	2.69 (1.99, 3.38)	NA
Two-sided *P* value (vs eculizumab)	<.0001[a]	NA	<.0001[a]	NA

Abbreviation: Diff = difference; ITT = intent-to-treat; LS = least-square; MMRM = mixed model for repeated measures; NA = not applicable.
Notes: Baseline is the average of measurements recorded before taking the first dose of pegcetacoplan, which will include local and central laboratory values during the screening period.
Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where Strata is the combination of stratification factors number of transfusions and platelet count at screening.
Data excluded from the absence of transfusions model: All values after intercurrent events were set to missing.
[a] Significant at the .05 α level.
Source: Table 14.2.1.1.2; Table 14.2.1.3.1.

Table 30: Summary for Number of Subjects With Transfusion Avoidance During Randomized Controlled Period by Number of PRBC Transfusion Prior to Baseline (ITT Set)

Transfusions Avoidance	Statistics	Pegcetacoplan (N = 20)	Eculizumab (N = 16)
Number of PRBC transfusion prior to baseline: <4			
Yes (no transfusion)	n (%)	17 (85.0)	5 (31.3)
No	n (%)	3 (15.0)	11 (68.8)
Received at least one transfusion[a]	n (%)	2 (66.7)	11 (100)
Withdrew from the study without having had a transfusion[a]	n (%)	1 (33.3)	0
Difference in percentage (pegcetacoplan - eculizumab)	Risk difference 95% CI	0.5375 0.2617, 0.8133	NA
Number of PRBC transfusion prior to baseline: ≥4			
		Pegcetacoplan Group (N = 21)	**Eculizumab Group (N = 23)**
Yes (no transfusion)	n (%)	18 (85.7)	1 (4.3)
No	n (%)	3 (14.3)	22 (95.7)
Received at least 1 transfusion[a]	n (%)	3 (100)	22 (100)
Withdrew from the study without having had a transfusion[a]	n (%)	0	0
Difference in Percentage (pegcetacoplan - eculizumab)	Risk Difference 95% CI	0.8137 0.6424, 0.9850	NA

Abbreviations: ITT = intent-to-treat; NA = not applicable; PRBC = packed red blood cells; RCP = randomized controlled period.
Transfusion avoidance is the proportion of subjects who do not require a transfusion during the RCP
Subjects who experienced more than 1 transfusion during RCP is only counted as once.
Subjects who have not had a transfusion but withdraw before Week 16 will be considered as having a transfusion in the analysis of transfusion avoidance.
[a] Percentages are based on the number of subjects in No category for each column.
The 95% CI for difference in percentage between treatments is constructed using the asymptotic method.
Source: Table 14.2.2.4.4.

Table 31: Summary for Number of Subjects With Transfusion Avoidance During Randomized Controlled Period by Number of Platelets Prior to Baseline (ITT Set)

Transfusions avoidance	Statistics	Pegcetacoplan group (N = 12)	Eculizumab group (N = 9)
Number of platelets prior to baseline: <100,000/mm³			
Yes (no transfusion)	n (%)	10 (83.3)	0
No	n (%)	2 (16.7)	9 (100)
Received at least 1 transfusion[a]	n (%)	1 (50.0)	9 (100)
Withdrew from the study without having had a transfusion[a]	n (%)	1 (50.0)	0
Difference in percentage (pegcetacoplan - eculizumab)	Risk Difference 95% CI	0.8333 0.6225, 1.0000	NA
Number of platelets prior to baseline: ≥100,000/mm³			
		Pegcetacoplan group (N = 29)	**Eculizumab group (N = 30)**
Yes (no transfusion)	n (%)	25 (86.2)	6 (20.0)
No	n (%)	4 (13.8)	24 (80.0)
Received at least 1 transfusion[a]	n (%)	4 (100)	24 (100)
Withdrew from the study without having had a transfusion[a]	n (%)	0	0
Difference in Percentage (pegcetacoplan - eculizumab)	Risk Difference 95% CI	0.6621 0.4717, 0.8524	NA

Abbreviations: ITT = intent-to-treat; NA = not applicable; RCP = randomized controlled period.
Transfusion avoidance is the proportion of subjects who do not require a transfusion during the RCP
Subjects who experienced more than one transfusion during RCP is only counted as once.
Subjects who have not had a transfusion but withdraw before Week 16 will be considered as having a transfusion in the analysis of transfusion avoidance.
[a] Percentages are based on the number of subjects in No category for each column.
The 95% CI for difference in percentage between treatments is constructed using the asymptotic method.
Source: Table 14.2.2.4.5.

Table 32: MMRM Model: Changes From Baseline in Reticulocyte Count During Randomized Controlled Period—Uncensored for Transfusions (ITT Set)

	Pegcetacoplan (N = 41) LS mean (SE) (10^9 cells/L)	Eculizumab (N = 39) LS mean (SE) (10^9 cells/L)	Difference (95% CI) in LS mean (vs eculizumab) (10^9 cells/L)	Nominal *P* value
Week 2	−147.52 (5.969)	−122.51 (6.367)	−25.01 (−41.23, −8.79)	.0030
Week 4	−136.49 (10.386)	29.34 (10.787)	−165.82 (−195.06, −136.59)	<.0001
Week 6	−131.48 (8.450)	1.31 (8.765)	−132.79 −156.30, −109.28)	<.0001
Week 8	−128.05 (9.409)	−1.28 (9.581)	−126.77 (−152.86, −100.68)	<.0001
Week 12	−128.91 (8.470)	−11.54 (8.530)	−117.37 (−140.54, −94.19)	<.0001
Week 16	−132.54 (9.023)	4.42 (9.146)	−136.96 (−161.87, −112.05)	<.0001

Abbreviations: ITT = intent-to-treat; LS = least-square; MMRM = mixed model for repeated measures.
Notes: Baseline is the average of available measurements recorded from central laboratory before taking the first dose of pegcetacoplan.
Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where Strata is the combination of stratification factors number of transfusions and platelet count at screening.
Source: Table 14.2.3.2.4.

Table 33: MMRM Model: Changes From Baseline in LDH During Randomized Controlled Period—Uncensored for Transfusion (ITT Set)

	Pegcetacoplan (N = 41) LS mean (SE) U/L	Eculizumab (N = 39) LS mean (SE) U/L	Difference (95% CI) in LS mean (vs eculizumab) U/L	Nominal *P* value
Week 2	−99.91 (29.276)	91.76 (31.352)	−191.66 (−272.64, −110.69)	<.0001
Week 4	−69.55 (22.605)	40.48 (24.184)	−110.02 (−170.97, −49.07)	.0010
Week 6	−35.97 (37.447)	29.40 (37.472)	−65.37 (−691.73, 560.99)	.4212
Week 8	−31.00 (33.883)	24.69 (34.993)	−55.70 (−151.07, 39.68)	.2393
Week 12	−50.18 (23.122)	−15.78 (23.981)	−34.39 (−93.03, 24.24)	.2496
Week 16	−43.44 (40.547)	41.73 (39.611)	−85.17 (−192.91, 22.57)	.1207

Abbreviations: ITT = intent-to-treat; LS = least-square; MMRM = mixed model for repeated measures.
Notes: Baseline is the average of available measurements recorded from central laboratory before taking the first dose of pegcetacoplan.
Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening.
Source: Table 14.2.4.2.4.

Table 34: MMRM Model: Changes From Baseline in FACIT-Fatigue Score During Randomized Controlled Period—Uncensored for Transfusion (ITT Set)

	Pegcetacoplan (N = 41) LS mean (SE)	Eculizumab (N = 39) LS mean (SE)	Difference (95% CI) in LS mean (vs eculizumab)	Nominal *P* value
Estimates/Comparisons at Week 2	11.14 (1.230)	0.69 (1.315)	10.45 (7.05, 13.84)	<.0001
Estimates/Comparisons at Week 4	9.03 (1.452)	−3.76 (1.541)	12.78 (8.73, 16.83)	<.0001
Estimates/Comparisons at Week 6	8.17 (1.411)	−1.29 (1.490)	9.46 (5.54, 13.38)	<.0001
Estimates/Comparisons at Week 8	10.51 (1.305)	−0.32 (1.375)	10.83 (7.25, 14.42)	<.0001
Estimates/Comparisons at Week 12	10.34 (1.316)	−0.71 (1.372)	11.04 (7.45, 14.64)	<.0001
Estimates/Comparisons at Week 16	9.65 (1.409)	−1.69 (1.466)	11.34 (7.47, 15.22)	<.0001

Abbreviations: FACIT = Functional Assessment of Chronic Illness Therapy; ITT = intent-to-treat; LS = least square; MMRM = mixed model for repeated measures.
Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan.
Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening.
Source: Table 14.2.5.2.4.

Others analyses by subgroups

The 2 treatment groups were generally similar at baseline with regard to number of subjects in each subgroup. No subjects in the eculizumab group were of Black/African American race, and 1 subject in the eculizumab group identified as Race: Other.

Subgroup analyses by sex showed that men in the pegcetacoplan group had a mean CFB at Week 16 that was approximately 1 g/dL greater than that of women in the pegcetacoplan group.

The mean CFB at Week 16 in the eculizumab group was similar for women and men.

Subgroup analyses by race showed that the greatest mean CFB in Hb at Week 16 in the pegcetacoplan group was seen in White subjects. Asian and Black/African American subjects in the pegcetacoplan group had a mean CFB that was approximately 1 g/dL lower than for White subjects.

By age, subjects in the pegcetacoplan group were comparable in mean CFB at Week 16.

Despite these differences, all pegcetacoplan subgroups achieved at least a 2 g/dL increase in Hb by Week 16.

Meaningful subgroup comparisons were not possible for the eculizumab arm given the large number of subjects who were removed from the analysis because of transfusions.

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 35. Summary of Efficacy for trial APL2-302

Title: A phase 3, randomized, multicenter, open-label, active-comparator controlled study to evaluate the efficacy and safety of pegcetacoplan in patients with paroxysmal nocturnal hemoglobinuria (pnh)

Study identifier	APL2-302, EudraCT: 2017-004268-36, ClinicalTrials.gov: NCT03500549		
Design	APL2-302 study is a global, Phase 3, prospective, randomized, multicenter, open-label, active comparator controlled study. The treatment period of the study consisted of a run-in period, a randomized controlled period (RCP), and an open-label period. Day 1 to Week 16 was defined as the RCP, over which endpoints were assessed. *This report presents data through Week 16.*		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		16 weeks 4 weeks 32 weeks
Hypothesis	Superiority		
Treatments groups	pegcetacoplan		twice-weekly SC doses of 1080 mg 16 weeks, n=41
	eculizumab		Varied doses, varied dosing schedules, administered intravenously. 16 weeks, n=39
Endpoints and definitions	Primary endpoint	CFB to Week 16 in Hb level	Change from baseline (CFB) to Week 16, excluding data before the randomized controlled period (RCP), in hemoglobin (Hb) level
	Key Secondary endpoint	Transfusion avoidance	Transfusion avoidance (Yes/No), defined as the proportion of subjects who do not require a transfusion during the study during the RCP
	Key Secondary endpoint	CFB to Week 16 in ARC	CFB to Week 16, excluding data before the RCP, in absolute reticulocyte count (ARC)
	Key Secondary endpoint	CFB to Week 16 in LDH	CFB to Week 16, excluding data before the RCP, in lactate dehydrogenase (LDH) level
	Key Secondary endpoint	CFB to Week 16 in FACIT-Fatigue Scale score	CFB to Week 16, excluding data before the RCP, in FACIT-Fatigue Scale score, Version 4
	Secondary endpoint	Hemoglobin response	Hemoglobin response in the absence of transfusions (Yes/No). Hemoglobin response of at least ≥1 g/dL in Hb from Baseline at Week 16, excluding data before the RCP
	Secondary endpoint	Reticulocyte normalization	Reticulocyte normalization in the absence of transfusions (Yes/No). Reticulocyte normalization is defined as the ARC being below the upper limit of the normal range at Week 16
	Secondary endpoint	CFB to Week 16, in indirect bilirubin level	CFB to Week 16, excluding data before the RCP, in indirect bilirubin level

	Secondary endpoint	CFB to Week 16, in haptoglobin level	CFB to Week 16, excluding data before the RCP, in haptoglobin level
	Secondary endpoint	CFB to Week 16, in LASA scores	CFB to Week 16, excluding data before the RCP, in Linear Analog Scale Assessment (LASA) scores
	Secondary endpoint	CFB to Week 16, in QLQ-C30 scores	CFB to Week 16, excluding data before the RCP, in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 Scale (QLQ-C30) scores
	Secondary endpoint	Number of PRBC units transfused during the RCP	Number of packed red blood cell (PRBC) units transfused during the RCP [>Day 1 to Week 16 and Week 4 to Week 16]
Database lock	24 December 2019		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat including all subjects who were randomized Week 16		
Descriptive statistics and estimate variability	Treatment group	pegcetacoplan	eculizumab
	Number of subject	41	39
	CFB to Week 16 in Hb level Least-square (LS) mean g/dl± SE	2.37 ± 0.363	-1.47 ± 0.666
	Transfusion avoidance % proportion of subjects	85.4	15.4
	CFB to Week 16 in ARC LS mean (10^9 cells/L)± SE	-135.82 ± 6.543	27.79 ± 11.859

	CFB to Week 16 in LDH LS mean U/L ± SE	-14.76 ± 42.708	-10.12 ± 71.025
	CFB to Week 16 in FACIT-Fatigue Scale score LS mean ± SE	9.22 ± 1.607	-2.65 ± 2.821
	Hemoglobin response % proportion of subjects	75.6	0
	Reticulocyte normalization % proportion of subjects	78.0	2.6
	Hemoglobin normalization % proportion of subjects	34.1	0
	CFB to Week 16, in indirect bilirubin level LS mean µmol/L ± SE	-17.78 ± 2.727	4.15 ± 4.477
	CFB to Week 16, in haptoglobin level LS mean g/L ± SE	-0.02 ± 0.033	0.12 ± 0.063
	CFB to Week 16, in LASA scores LS mean ± SE	49.38 ± 10.189	-9.72 ± 18.988
	CFB to Week 16, in QLQ-C30 LS mean ± SE	15.91 ± 3.635	-2.71 ± 8.515
	Number of PRBC units transfused during the RCP Mean (SD)	0.6 ± 2.03	5.1 ± 5.60

Effect estimate per comparison	Primary endpoint	Comparison groups	pegcetacoplan *vs.* eculizumab
		Difference in LS mean; mixed-effect model for repeated measures (MMRM)	3.84
		95% CI	2.33, 5.34
		P-value (superiority test)	P<0.0001
	Transfusion avoidance	Comparison groups	pegcetacoplan vs. eculizumab
		Risk difference	0.6253
		95% CI	0.4830, 0.7677
		P-value (non-inferiority test)	P<0.0001
	CFB to Week 16 in ARC	Comparison groups	pegcetacoplan vs. eculizumab
		Difference in LS mean (109 cells/L); MMRM	-163.61
		95% CI	-189.91, -137.30
		P-value (NI test)	P<0.0001
	CFB to Week 16 in LDH	Comparison groups	pegcetacoplan vs. eculizumab
		Difference in LS mean (U/L); MMRM	-4.63
		95% CI	-181.30, 172.04
		P-value (NI test)	P=0.9557
	CFB to Week 16 in FACIT-Fatigue Scale score	Comparison groups	pegcetacoplan vs. eculizumab
		Difference in LS mean (U/L); MMRM	11.87
		95% CI	5.49, 18.25
		P-value (NI test)	P=0.0005
	Hemoglobin response	Comparison groups	pegcetacoplan vs. eculizumab
		Difference in percentage	0.6745
		95% CI	0.5452, 0.8039
	Reticulocyte normalization	Comparison groups	pegcetacoplan vs. eculizumab
		Difference in percentage	0.6639
		95% CI	0.5309, 0.7968
	Hemoglobin normalization	Comparison groups	pegcetacoplan vs. eculizumab
		Difference in percentage	0.3043
		95% CI	0.1493, 0.4593

	CFB to Week 16, in indirect bilirubin level	Comparison groups	pegcetacoplan vs. eculizumab
		Difference in LS mean (µmol/L); MMRM	-21.93
		95% CI	-32.49, -11.36
	CFB to Week 16, in haptoglobin level	Comparison groups	pegcetacoplan vs. eculizumab
		Difference in LS mean (g/L); MMRM	-0.14
		95% CI	-0.28, -0.01
	CFB to Week 16, in LASA scores	Comparison groups	pegcetacoplan vs. eculizumab
		Difference in LS mean; MMRM	59.10
		95% CI	16.88, 101.32
	CFB to Week 16, in QLQ-C30	Comparison groups	pegcetacoplan vs. eculizumab
		Difference in LS mean; MMRM	18.62
		95% CI	0.12, 37.13
	Number of PRBC units transfused during the RCP Mean	Comparison groups	pegcetacoplan vs. eculizumab
		Mean (SD)	0.6 (2.03) vs. 5.1 (5.60)
		95% CI	2.0, 4.0 vs. NA
Notes	To preserve the Type 1 error rate, the key secondary endpoints were tested in a hierarchical manner after statistical significance was reached for the primary endpoint. Once one hypothesis tested not significant, all subsequent tests were not assessed.		

2.6.5.3. Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled trials[a]	7/41	3/41	0/41
Non Controlled trials[b]	2/35	0/35	0/35

a Includes Study APL2-302.
b Includes Studies 202, 204, and CP0514.

2.6.5.4. Supportive studies

APL2-202 study

A phase 2a, open-label, multiple dose study to assess the safety, efficacy, and pharmacokinetics of subcutaneously administered pegcetacoplan in subjects with PNH

Primary endpoints were efficacy endpoints: CFB in LDH, haptoglobin level and hemoglobin levels

Methodology: A single cohort of subjects was planned for evaluation. The study was closed for enrolment by the sponsor after 4 subjects were enrolled.

All subjects in this study received pegcetacoplan 270 mg/day. Patients showing evidence of clinical benefit could receive pegcetacoplan daily until Day 364.

Main inclusion criteria: Subjects were at least 18 years old who were diagnosed with PNH, LDH levels ≥2 times the ULN and had received a transfusion within 12 months prior to screening. Subjects were excluded if they had received prior eculizumab.

Efficacy results:

Mean LDH level at baseline was 2548.8 U/L. Lactate dehydrogenase levels remained lower than baseline through Day 365 (mean CFB −2322.8 U/L). Three subjects (75%) had LDH ≤ULN, and all 4 subjects (100%) had LDH values ≤1.5× the ULN at Day 365.

Mean haptoglobin level at baseline was 0.1 g/L. Mean haptoglobin at Day 365 was 0.18 g/L (mean CFB 0.08 g/L).

Mean hemoglobin (Hb) level at baseline was 7.73 g/dL. Mean Hb level remained above baseline through Day 365 (mean CFB 5.27 g/dL). Three subjects had Hb levels ≥LLN at Day 365. One subject had a mean Hb level of 10.14 g/dL, which was just outside of the normal range (LLN 11.6 g/dL).

Mean FACIT-Fatigue score at baseline was 40.5. At Day 365 the mean score was 47.0 (mean CFB 6.5), and all subjects except 1 showed an improvement in score from baseline at Day 365.

Mean ARC at baseline was 238.3/nL. Mean ARC remained below baseline through Day 365 (mean CFB −144.3/nL). Three subjects (75%) had ARCs ≤ULN at Day 365.

Mean total bilirubin at baseline was 30.85 µmol/L. At Day 365 the mean CFB was −21.53 µmol/L. Three subjects (75%) had bilirubin levels ≤ULN, and all 4 subjects (100%) had a bilirubin level ≤1.5 × ULN at Day 365.

No subject required a transfusion during the study. All 4 subjects were transfusion-dependent prior to entering the study, with a transfusion history ranging from 2 to 9 PRBC transfusions in the prior year.

All subjects except 1 showed an increase in total LASA score baseline at Day 365. Two subjects had an increase from baseline at Day 365 of greater than 100 points.

In conclusion, these data should be taken with cautions as based on only 4 subjects. Pegcetacoplan at the dose of 270 mg daily showed preliminary efficacy results in patients who had not already received eculizumab.

APL2-CP-PNH-204 study

A phase 1b, open-label, multiple ascending dose, pilot study to assess the safety, preliminary efficacy and pharmacokinetics of subcutaneously administered pegcetacoplan in subjects with PNH

Primary endpoints were efficacy and safety endpoints.

The primary efficacy endpoints were CFB and percentage CFB in LDH, haptoglobin, and Hb.

The secondary efficacy endpoints were CFB in FACIT-Fatigue score, CFB and percentage CFB in ARC and total bilirubin level, and number of RBC transfusions per month.

Methodology: The study was planned to enroll approximately 23 subjects: 3 subjects in Cohort 1 and up to 20 subjects in Cohort 2. Subjects could participate in more than 1 cohort.

Dosage: 180 mg/day in Cohort 1 or 270 mg/day (increasable up to 360 mg/day if clinically indicated on the basis of response) in Cohort 2, administered SC. Patients showing evidence of clinical benefit could receive pegcetacoplan daily until Day 364.

Main criteria: Subjects were aged ≥18 years with PNH, LDH ≥2 times the ULN, and have had their last transfusion within 12 months prior to screening. Subjects who had received prior eculizumab treatment were excluded from the study.

Efficacy results:

Six subjects discontinued from the study: 3 subjects withdrew consent for reasons not related to safety, 2 subjects discontinued because of an AE, and 1 subject discontinued because of physician decision.

Table 36: Overall Subject Disposition—Screened Set

	Cohort 1 (N = 3)	Cohort 2 (N = 20)	Total (N = 22)
Screened			26
Subjects entering both cohorts			1 (3.8%)
Enrolled	3 (100%)	20 (100%)	22 (84.6%)
Completed study per protocol	2 (66.7%)	15 (75.0%)	17 (77.3%)

Treatment with 270 mg/day pegcetacoplan resulted in improvements in hematologic parameters. Change from baseline in mean Hb was 3.68 g/L at Day 365. Change from baseline in mean haptoglobin was 0.066 g/L at Day 365.

Change from baseline in mean LDH was −2105.2 U/L at Day 365. Change from baseline in mean total bilirubin was −29.9 µmol/L at Day 365.

Change from baseline in mean ARC was −105.9 × 109 cells/L at Day 365.

Two of the 3 subjects in Cohort 1 and 13 of the 20 subjects in Cohort 2 did not require transfusions during the pegcetacoplan dosing period. Three additional subjects (1 in Cohort 1 and 2 in Cohort 2) received their only dosing-period transfusion prior to pegcetacoplan reaching a steady-state concentration (Days 2, 3, and 15). Transfusion in the other 5 subjects in Cohort 2 were associated with SAEs.

Change from baseline in mean FACIT-Fatigue score was 7.1 points at Day 365. An increase in mean FACIT-Fatigue score of ≥3 points is generally accepted as clinically meaningful.

In conclusion, these efficacy data should be considered as descriptive data as this phase 1b was an open-label and multiple ascending dose. Among these subjects who had not already received eculizumab, 2 subjects received pegcetacoplan at 180 mg daily dose and 13 received pegcetacoplan at 270 mg daily dose. Preliminary efficacy data showed efficacy in these patients (increase of CFB in mean Hb, reduction in hemolysis (reduction in LDH and total bilirubin), reduction of CFB in mean ARC, increase in mean FACIT-Fatigue score.

APL-CP0514 study

A phase 1 open-label, single and multiple ascending dose study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of APL-2 as an add-on to standard of care in subjects with PNH

Methodology:

Only efficacy exploratory endpoints were assessed as dependence of transfusion and FACIT-Fatigue score.

Four cohorts of 12 subjects overall (9 unique subjects) with PNH who were still anemic during treatment with eculizumab (Soliris®) were evaluated. SC administration of APL-2 was evaluated in a single-dose phase and multiple-dose phase in Cohorts 1 and 2 (2 subjects each) and in multiple-dose phase only in Cohorts 3 (2 subjects) and 4 (6 subjects). Subjects could participate in more than 1 cohort.

The 4 cohorts were treated as follows:

- Cohort 1: Single SC dose of 25 mg APL-2 on Day 1, then, following a waiting period of at least 28 days, daily 5-mg SC dose of APL-2 for 28 days.

- Cohort 2: Single SC dose of 50 mg APL-2 on Day 1, then, following a waiting period of at least 28 days, daily 30-mg SC dose of APL-2 for 28 days.

- Cohort 3: Daily 180-mg SC dose of APL-2 for 28 days.

- Cohort 4: Daily SC dose of 270 mg APL-2 for up to 729 days with optional intrasubject escalation up to 360 mg/day after Day 28.

Main Criteria for Inclusion: Subjects were at least 18 years old. Subjects had to be diagnosed with PNH, on treatment with eculizumab for at least 3 months, and hemoglobin < 10 g/dL at Screening OR have received at least 1 transfusion within 12 months prior to Screening.

Efficacy results:

FACIT score increased for all subjects in Cohort 3 and Cohort 4, except the subject in Cohort 4 who already had a high value at baseline. In general, FACIT Fatigue Total Score among Cohort 4 subjects increased from baseline and levels were maintained over the course of the study. At the end of the study (Week 105), Cohort 4 subjects had a mean CFB of +9.0 (range 1 to 18).

Only 1 subject in Cohort 4 had a transfusion while receiving APL-2. Across the cohorts transfusions were mainly either before APL-2 had reached steady state, during dosing interruptions, or following discontinuation of study treatment.

Data were based on only 9 subjects as the study was closed for enrolment. No conclusion could be drawn based on these data.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Clinical development programme for pegcetacoplan in patients with PNH includes 6 clinical studies. Two of those studies are ongoing and not submitted within this MAA. Out of the 4 remaining clinical studies, 3 are designated as supportive and 1 is designated pivotal. The supportive studies are Study APL2-CP-PNH-204 (Study 204; Paddock), Study APL2-202 (Study 202; Palomino) and Study APL-CP0514 (Study CP0514; Pharoah). Those 3 studies are early-phase (204: Phase 1b; 202: Phase 2a; CP0514: Phase 1b), uncontrolled, with a very limited sample size of different PNH populations included (Study 204: 20 C5i-naïve subjects; Study 202: 4 C5i-naïve subjects; Study CP0514: 6 C5i-treated subjects). Therefore, the impact of supportive studies on this application is limited.

Supportive studies did not include the same pegcetacoplan dosing regimen as the pivotal Study APL2-302, although adequate systemic exposure to pegcetacoplan was reached with the dosing used (270

mg/d up to 360 mg/d). Dosing regimen used in the pivotal trial (1080 mg twice weekly) was chosen based on these supportive studies and PK modelling.

Study design (main study)

Study APL2-302 is considered the pivotal study to provide the evidence of efficacy and safety. This study is a global, Phase 3, prospective, randomized, multicenter, open-label, active comparator controlled study. Its objective is to confirm treatment efficacy and safety of pegcetacoplan monotherapy for the treatment of PNH in subjects aged ≥18 years who were receiving eculizumab therapy but continued to have Hb levels <10.5 g/dL. Subjects were randomized to receive pegcetacoplan 1080 mg twice weekly or every 3 days if clinically indicated or their current dosage of eculizumab. This head-to-head comparator trial was designed to demonstrate superiority of pegcetacoplan to eculizumab monotherapy in subjects with PNH currently on treatment with eculizumab as measured by change in Hb level at Week 16. After completion of the RCP (the end of Week 16), subjects continue into a 32-week open-label pegcetacoplan period in which all subjects receive twice-weekly doses of pegcetacoplan 1080 mg. The 16-week RCP is completed; the 32-week open-label period is ongoing. The clinical study report (CSR) covers data through the 16-week RCP.

In total, 80 subjects were randomised (1:1) to either pegcetacoplan or eculizumab. Randomisation was stratified (per Protocol Amendment 3 Version 1.0) according to number of PRBC transfusion events within 12 months prior to Day -28 (<4; ≥4) and according to platelet count (<100,000; ≥100,000). Since the initial stratification factor of transfusion history was significantly different (it was based on the number of units of PRBC transfused as opposed to the number of events of transfusion that was introduced with the Protocol Amendment), the Applicant was requested to discuss the impact of these changes. A discussion on the rationale for a change and possible impact has been provided. According to the Applicant, introduced protocol amendments did not significantly impact study results and conclusions. Different eligibility criteria were changed in order to reflect emerging PK data or to better capture the effectiveness of pegcetacoplan. Key secondary outcome (transfusion avoidance) was introduced and other secondary and tertiary outcomes were rearranged; data were analysed according to amended SAP.

Another issue from the Protocol Assistance that was not adhered to is a strong recommendation to randomise before run-in and not afterwards, as a pre-selection (e.g., depending on APL-2 tolerance and/or early efficacy) can otherwise not be excluded. A relevant discussion on the time-point for randomisation has been provided by the Applicant. It is acknowledged that the Applicant has thought through this issue, and that neither time-point for randomisation is flawless. From the CHMP's point of view, randomisation after run-in period raises concerns about possible selection bias. However, no subject discontinued during the run-in period, and that the length of run-in period matches time to reach therapeutic concentrations of pegcetacoplan.

As raised in the protocol assistance on 6 November 2017 by the Applicant (EMEA/H/SA/3633/1/FU/1/2017/PA/SME/II), assessing the response to therapy at 16 weeks might not be sufficient to establish a benefit risk balance long-term, particularly given the long life span of red cells (approximately 12-16 weeks). It was noted that the treatment effect on the primary endpoint is quite clear at 16-weeks; however, there was a need to obtain long-term effect data of pegcetacoplan. As part of the responses to the LoQ, the applicant submitted efficacy and safety data from the Study APL2-302 OLP from Week 17 through Week 48 + follow-up with a data cut-off date of 23 September 2020.

Population

Study APL2-302 included adult PNH patients currently being treated with eculizumab (having a stable dose of eculizumab for at least 3 months) but who continued to be anaemic (haemoglobin level <10.5 g/dL at screening) despite receiving eculizumab. Therefore, the pivotal trial examined pegcetacoplan as a second-line treatment.

Some imbalances were observed between pegcetacopan and eculizumab groups regarding baseline clinical characteristics - fewer subjects in pegcetacoplan vs eculizumab arm were on label dose of eculizumab at baseline (63.4% and 76.9%). More participants in eculizumab group had ⩾4 transfusion in the last 12 months compared to pegcetacoplan (59% compared to 51.2%). Mean LDH levels were higher in the eculizumab group compared to pegcetacoplan (309 compared to 257, respectively). Haptoglobin levels were more profoundly reduced in eculizumab group (0.125 compared to 0.144 in the pegcetacoplan group). Some of these imbalances suggest that patients in eculizumab group might have less controlled disease.

Treatments

During the RCP, patients were receiving either pegcetacoplan 1080 mg twice weekly or their current dose of eculizumab. Pegcetacoplan is administered subcutaneously and this could be done by the patients themselves (or a caregiver), while eculizumab is administered intravenously by a healthcare provider.

During the RCP, dose of pegcetacoplan could be adjusted (from 1080 mg twice weekly to 1080 mg every third day) if LDH during pegcetacoplan monotherapy was >2 × ULN. The Applicant provided an extended analysis as a justification for dose adjustments.

Endpoints

The primary efficacy endpoint was change from baseline (CFB) to Week 16, excluding data before the randomized controlled period (RCP), in hemoglobin (Hb) level. Key secondary endpoints were: transfusion avoidance, CFB in absolute reticulocyte count (ARC), CFB in LDH and CFB in FACIT-Fatigue Scale score. A number of other secondary efficacy endpoints were pre-specified.

From a clinical standpoint, transfusion avoidance is a crucially important endpoint. This outcome was also used as an endpoint in other PNH studies. Different approaches to transfusion in different centres were harmonised by using a pre-specified protocol criteria describing when to give a transfusion (if Hb value is <7 g/dL without symptoms or <9 g/dL with symptoms).

Overall, the endpoints are clinically relevant and appropriate for the study.

Statistical Plan

Superiority of pegcetacoplan over eculizumab was examined for the primary outcome. Non-inferiority was used to compare results for the key secondary outcomes, while superiority was used for other secondary outcomes. Key secondary outcomes were tested in a hierarchical manner, with formal testing stopping after a non-significant result was observed.

Efficacy analyses were performed using the ITT as the primary efficacy population. Since the ITT and PP populations are equally important in analysing non-inferiority trials, analyses of the key secondary outcomes on the PP population are of high importance.

Transfusions were intercurrent events (ICE) in Study 302. When a subject had a transfusion during the RCP, their data collected after the transfusion were excluded (i.e. set to missing) from the calculation for all efficacy endpoints and measurements up to the level of transfusion were included in analyses, representing a while-on-treatment strategy. The Applicant presented time-to-transfusion data including Kaplan-Meier plots as requested. There was a marked difference in time to transfusion in the eculizumab group vs pegcetacoplan group that has to be taken into consideration when interpreting study results. Time to discontinuation did not reveal significant difference between the study groups.

The between-treatment-group comparison for the primary efficacy endpoint was performed using a mixed-effect model for repeated measures (MMRM) (Mallinckrodt et al. 2008). The primary analysis model relies on the assumption of Missingness At Random (MAR). Mixed model approach is likely a more

reliable method for the estimation of primary endpoint as opposed to simple statistical imputation methods, therefore this type of analysis for the primary outcome is suitable.

The use of a mixed model for repeated measures (MMRM) in the primary analysis is consistent with the while-on-treatment estimand strategy chosen by the Applicant. All Hb level available until intercurrent events (transfusion, treatment discontinuation and withdrawal) or week 16 have been used to calculating the change from baseline in patients, therefore, no missing data has been imputed in the primary analysis.

Two sensitivity analyses for the primary outcome are planned as a 'departure from the MAR assumption towards the Missingness Not At Random (MNAR) assumption'– Controlled-Based Pattern Imputation and a Tipping point analysis. These sensitivity analyses are endorsed. However, additional sensitivity analyses to investigate different MNAR scenarios are warranted as per Guideline on Missing data in confirmatory clinical trials (EMA/CPMP/EWP/1776/99 Rev. 1). Additional sensitivity analyses to investigate different MNAR scenarios were done as requested. It is agreed that analyses under different assumptions and utilising different methods for handling missingness led to similar conclusions.

Due to the favorable outcomes observed on these key endpoints, the absence of clinically relevant information on these margins is not an issue.

Conduct

The numbers of subjects in the run-in set, ITT set, mITT set, and safety set are identical. Numbers of patient's withdrawals are well-balanced in both arms. No treatment allocation errors occurred in the trial. Reasons for protocol amendments are well described and may not impact efficacy endpoints. High rates of protocol deviations were observed in both arms (97.6 vs. 97.4%). Most major protocol deviations (45 subjects; 56.3%) involved study assessments/schedule noncompliance. Reasons for these deviations included missed timing for laboratory or vital signs collection, missed visits, missed vaccinations, and assessments not completed by the subject.

Of particular importance are major protocol deviations regarding nonadherence to protocol-specified criteria for PRBC transfusion since all of them occurred in eculizumab arm. The Applicant has clarified that two participants in eculizumab group received transfusion despite not meeting the protocol-specified criteria, and the third participant did not receive transfusion despite meeting the criteria for it. The Applicant reassessed all protocol deviations during the end-of-study APL2-302 activities and identified additional case of receiving transfusion despite not meeting the protocol-specified criteria. In total, 3 participants in eculizumab group received transfusion despite not meeting the criteria, two of which were excluded from the PP set of 16-week CSR. Those 3 cases were classified as a major protocol deviations. The fact that 3 patients in eculizumab arm received a transfusion despite their pretransfusion haemoglobin levels being >9.0 g/dL is troublesome. Subject 01009002 received the transfusion on Study Day 106 of the RCP, which is near the end of the RCP period, while Subject 06001006 received the transfusion on Study Day -53, which is during screening. Therefore, it can be agreed that the impact of these occurrences on study results is limited. The newly recognized patient to receive the transfusion despite not meeting criteria (Subject 04001007) received it early on during the RCP, on Day 24, which might influence the study results. The Applicant provided additional sensitivity analysis excluding this patient form the PP set and the results are in line with the primary results.

The Applicant did a re-categorisation of protocol deviations in Dec 2020 as an end-of-study activity (it was identified that the implementation of study-specific Protocol deviation guidance document had resulted in operational non-compliance deviations being categorized as major, despite not meeting the definition of significantly impacting subject safety and/or data integrity). It can be agreed that most of those deviations would not have significant impact on the study results and overall interpretation.

Nevertheless, it remains unfortunate to re-categorise protocol deviations after database lock date, as it raises concerns on the overall internal validity.

A GCP non-compliant site from the US that enrolled 2 patients was closed, but the patients were included in the ITT analysis. The Applicant provided requested details. The 2 participants' inclusion in the ITT set is questionable, but it can be considered justified. Sensitivity analysis provides confirmation of consistency with a main analysis.

Compliance with study treatments was high in both treatment arms throughout the run-in and the randomised period which is important considering the small sample size.

Efficacy data and additional analyses

The study enrolled 80 subjects. The numbers of subjects in the run-in set, ITT set, mITT set, and safety set are nearly identical (n=41 for pegcetacoplan arm and n=39 for eculizumab arm). 36 in pegcetacoplan arm and 35 patients in eculizumab arm were included in PP set.

Treatment groups were globally balanced with regards to age, sex, height, weight, ethnicity, and race. Mean age was 50.2 years in pegcetacoplan arm vs. 47.3 years in eculizumab arm. Elderly subjects (65 years and older) were included; however, experience with pegcetacoplan in Study APL2-302 in elderly subjects >65 years is limited to 17 subjects (21.3%).

There were more subjects in the eculizumab group (30.8%) from the APAC region (Australia, Japan, Russia, and South Korea) than in the pegcetacoplan group (14.6%). The EU region (Belgium, France, Germany, United Kingdom, and Spain) had more subjects in the pegcetacoplan group (61%) than in the eculizumab group (48.7%). The primary and key secondary endpoints analyses have been provided for the 3 following geographical regions investigated in the trial: APAC, EU and NA as requested.

Slightly less than one-third of subjects had a prior history of at least 1 type of thrombosis, including 15 subjects (36.6%) in the pegcetacoplan group and 10 subjects (25.6%) in the eculizumab group. The mean time since diagnosis of PNH to Day −28 was 10.18 years overall and was longer in the eculizumab group than in the pegcetacoplan group (11.68 years vs 8.74 years). The duration of prior eculizumab treatment was numerically similar between the 2 groups (1868.3 days vs. 1745.9 days).

The most common eculizumab dosing level and regimen was 900 mg every 2 weeks (70% of subjects), which is consistent with the approved product label. The remaining subjects were receiving higher than the label dose of eculizumab, or more frequent administration than the label specified. Specifically, 21 subjects (26.3%) were receiving 1200 mg every 2 weeks, 2 subjects (2.5%) were receiving 1500 mg every 2 weeks, and 1 subject (1.3%) was receiving 900 mg once every 11 days. Fewer subjects in the pegcetacoplan group than in the eculizumab group were on the label dose of eculizumab at baseline (63.4% and 76.9%). The 2 subjects who were taking the highest eculizumab dose at baseline (1500 mg twice weekly) were in the pegcetacoplan group.

Baseline mean Hb, platelet, ARC, haptoglobin, total bilirubin, indirect bilirubin, and FACIT-Fatigue score were generally similar between groups. LDH was slightly higher in the eculizumab group than in the pegcetacoplan group (308.64 vs 257.48, respectively). The mean number of transfusions in the last 12 months prior to Day −28 was similar between the 2 treatment groups. Overall, 55% of subjects had ≥ 4 PBRC transfusions in the year prior to Day-28. Slightly more subjects in the eculizumab group (59%) reported ≥ 4 PBRC transfusions than in the pegcetacoplan group (51.2%).

Mean compliance during RCP for subjects receiving eculizumab was 100%, and 99.94% for subjects receiving pegcetacoplan. During the RCP, there were only two subjects who increased dosing to every 3 days. The Applicant provided additional data from 13 patients experiencing dose escalation within OLP.

Dose increase for patients experiencing low pegcetacoplan levels around haemolysis during treatment with pegcetacoplan twice weekly is considered justified.

With the MMRM analysis, the least-square (LS) mean CFB in Hb at Week 16 in the pegcetacoplan and eculizumab groups was 2.37 g/dL and -1.47 g/dL, respectively. The difference in LS mean CFB in Hb between the 2 groups of 3.84 g/dL was statistically significant (95% CI 2.33, 5.34; P<.0001) and higher than the pre-specified difference between pegcetacoplan and eculizumab of 1 g/dl. The primary endpoint has been reached in this superiority trial. A large number of subjects received transfusions in eculizumab arm (n=33) compared to pegcetacoplan arm (n=5). These data reflect a superiority of pegcetacoplan compared to eculizumab in terms of efficacy of control of the disease. The Applicant has provided additional sensitivity analyses of primary efficacy endpoint (based on imputation methods) and supportive analyses of primary efficacy endpoint data with all available data (uncensored for transfusion) which confirm this primary analysis.

Regarding the key secondary endpoint, pegcetacoplan met noninferiority to eculizumab on transfusion avoidance, with 85.4% of pegcetacoplan subjects and 15.4% of eculizumab subjects achieving transfusion avoidance (nominal P value <.0001). This result is significantly clinically relevant. The proportion of subjects who were transfusion avoidant was similar in the pegcetacoplan group, regardless of baseline PRBC transfusion strata or baseline platelet strata, but not in the eculizumab group. Pegcetacoplan was also non-inferior to eculizumab for CFB in ARC, a marker of hematopoietic bone marrow compensatory activity in the setting of anemia and/or hemolysis, with an LS mean difference of −163.6 × 109 cells/L (nominal P value <.0001). LDH did not meet non-inferiority by the prespecified analysis. However, a greater percentage of subjects on pegcetacoplan achieved LDH normalization, as compared with eculizumab (71% vs 15%, respectively). Noninferiority for the FACIT-Fatigue score was not assessed because of the prespecified hierarchical testing. Of note, a higher numerical improvements were seen in FACIT-Fatigue score in the pegcetacoplan group as compared with the eculizumab group with a difference of 11.87 points (95% CI 5.49, 18.25; nominal P value .0005).

As part of the responses to the LoQ, the applicant submitted efficacy and safety data from the Study APL2-302 OLP from Week 17 through Week 48 + follow-up with a data cut-off date of 23 September 2020. All subjects had completed the Week 48 visit and had either entered follow-up or the extension study, Study APL2-307.

Data cut-off was set to 23 September 2020. This data cut includes 77 subjects who entered the open-label period (OLP) and 67 (87%) subjects who completed the Week 48 visit. Ten subjects (13.0%) discontinued from study treatment.

Results from OLP constitute additional data for long-term treatment efficacy after 16 weeks. Results of the key efficacy analyses of the OLP confirmed the results observed during the 16-week RCP.

Results suggest an improvement in PNH markers and fatigue and efficacy results were comparable to that observed for the pegcetacoplan continuation group when pegcetacoplan was added to eculizumab for subjects previously treated with eculizumab monotherapy after Week 16.

Improvements in FACIT-Fatigue score were confirmed through Week 48 with 55% of subjects improved FACIT-Fatigue score by ≥3 points. The PK analysis within OLP also showed that therapeutic concentrations of pegcetacoplan were maintained for up to Week 48.

Open-label design for a single pivotal study is considered a drawback, hence a double-dummy design was proposed in the Protocol Assistance (EMEA/H/SA/3633/1/FU/1/2017/PA/SME/II). The Applicant provided relevant discussion on exclusion of a double-dummy design, and it is acknowledged. However, the Applicant did not provide an assessment of the risk of bias in the single pivotal clinical trial as requested. Specific measures of minimisation of bias are outlined. It is considered that measures used to minimise the risk of bias preserved internal validity sufficiently.

A short discussion regarding the impact of investigators interventions and primary and secondary endpoints measurements' conditions has been provided. The applicant clarified that laboratory measures were conducted in the central laboratory and treatment assignment information was not communicated to this latter. The need of transfusions and the classification of patients as responders/non responders was done following objective lab tests criteria regardless of investigator opinion.

At the time of planning Study 302, eculizumab was the only approved therapy for PNH. Since July 2019 another C5 inhibitor (ravulizumab) is approved for the treatment of patients with PNH. Since eculizumab and ravulizumab share the same mechanism of action, it is acceptable to view the comparator in this study (eculizumab) as representing both available C5 inhibitors.

It is noted that TA was achieved in a very low number and percentage of subjects in the eculizumab arm (only 6 out of 39 patients, amounting to 15.4%). This seems to be an under-performace of eculizumab, since transfusion avoidance was reached in 51% of patients treated with eculizumab in the TRIUMPH and SHEPHERD trials (Soliris SmPC) and in 66.1% of eculizumab-treated patients in a recent study with ravulizumab (Lee et al., 2019). The Applicant provided relevant discussion and justification for apparent underperformance of eculizumab arm in the pivotal trial APL2-302. It is agreed that underperformance of eculizumab cannot easily be concluded because patient populations in the pegcetacoplan, eculizumab and ravulizumab pivotal trials were different. Some literature references provided are of limited value due to a small sample sizes but are supportive of conclusions.

The Applicant provided an extended analysis as a justification for dose adjustments. Data were collected in 15 patients in total, from whom 13 were enrolled in OLP. Escalation was decided after patients experiencing haemolytic events, elevated LDH value and a low pegcetacoplan concentration at the time of haemolysis under Pegcetacoplan twice weekly. No eculizumab dose adjustments was recorded however variations from the planned eculizumab dosing schedule have been reported with no associated haemolytic events or clinical impact.

Of the 15 patients, 8 (53.3%) have demonstrate benefit from Q3D dosing, 4 (26.7%) did not demonstrate benefit and 3 (20%), were not assessable because of limited Q3D treatment duration (<30 days). Based on data provided, it is endorsed that dose increase should be an option for patients experiencing low pegcetacoplan levels around haemolysis during treatment with pegcetacoplan twice weekly.

Improved outcomes with pegcetacoplan treatment, as compared with eculizumab treatment, were observed in others secondary endpoints at Week 16. Higher percentage of subjects in the pegcetacoplan group, as compared with the eculizumab group, achieving Hb response (75.6 % vs 0%), Hb normalization (34.1% vs 0%), and ARC normalization (78% vs 2.6%). Subjects in the pegcetacoplan group required fewer units of PRBCs to be transfused. The mean number of PRBC units required in the pegcetacoplan group was 0.6 and in the eculizumab group was 5.1 (95% CI: 2.0, 4.0). Indirect bilirubin levels decreased with pegcetacoplan treatment, but not with eculizumab treatment. LASA and QLQ-C30 scores increased in pegcetacoplan arm but not in eculizumab arm. An exception is noted with haptoglobin, which showed a further decrease (-0.02 g/L) in the pegcetacoplan group and an increase (0.12 g/L) in the eculizumab group from baseline to Week 16. In both groups the observed values of haptoglobin were below the LLN at week 16, with values in eculizumab group being closer to the LLN than values in pegcetacoplan group. The Applicant provided relevant discussion and possible explanation for observed differences in CFB in haptoglobin values between study groups, which is acknowledged. It seems that there was a number of censored observations in the eculizumab group.

When all observed data were considered (no censoring of data due to PRBC transfusion), the results of all primary and key secondary analyses were consistent with the MMRM analyses in which post-transfusion data were set to missing. This is reassuring; however for full interpretation the Applicant provided requested information regarding the amount of missing and imputed data in the uncensored

analysis information. MMRM uncensored analysis included subject with missing data, with no formal imputation. There was a notable difference in missing data between study groups. Despite the difference, the Applicant is claiming consistency of all obtained results. As stated in the initial assessment, this is an important analysis bearing in mind the large amount of censoring in the primary analysis, especially in eculizumab arm. Considering provided information on the missing data, the supportive analysis 1 of CFB in Hb levels at Week 16 (uncensored for transfusion) is found to be supportive, although the magnitude of observed benefit with pegcetacoplan compared to eculizumab is smaller than in the primary analysis, as already pointed out in the initial assessment.

Two sensitivity analyses for the primary outcome were performed. The first sensitivity analysis is the control-based pattern imputation (CBPI) censored for transfusion. In this analysis, it is assumed that participants who discontinue (in either group) will have unobserved outcomes similar to subjects in eculizumab arm (for details please see Main study assessment in clinical AR). In this analysis, LS mean difference in CFB in Hg (pegcetacoplan – eculizumab) was 2.60 g/dL (95% CI 1.59, 3.61; p<0.0001). The effect size is very similar to analysis with uncensored values, and smaller than the results of the primary analysis although still statistically significant and clinically relevant.

The second sensitivity analysis was the tipping point analysis, which shows that the true tipping point for LS mean difference in CFB in Hb (pegcetacoplan – eculizumab) is between 1.46 and 1.57 g/dL. This is quite below the effect size obtained with the primary analysis. However, this analysis also used data censored for transfusion.

The Applicant also provided CBPI and tipping point analyses while using all available data (no censoring for transfusion). These results are similar to when censored data are used. Therefore, the sensitivity analyses are supportive of the primary analysis of the primary efficacy outcome demonstrating superiority of pegcetacoplan over eculizumab.

The 5 supportive analyses (using uncensored data; mITT; PP; completers; nonparametric ANCOVA) were in line with the primary analysis.

Subgroup analyses according to gender and race show some differences across subgroups. Females in pegcetacoplan arm (23 evaluated) show a mean CFB in Hb of 2.44 g/dL while males in pegcetacoplan arm (13 evaluated) show a mean CFB in Hb of 3.42 g/dL. Such a difference is not observed in eculizumab arm. The Applicant provided discussion on the possible impact of gender and is claiming that apparent difference in haemoglobin CFB in men and women may by driven by the difference in haemoglobin LLN between sexes rather than by a difference in response to pegcetacoplan. Indeed, gender did not have clinically relevant effect on the pegcetacoplan PK based on the results of the popPK analysis (please refer to the initial PK assessment). Provided discussion might be plausible. Of note, number of subjects in eculizumab group analysed at Week 16 was too small for conclusions (female N=4, male N=2).

Subgroup analyses by race showed that the greatest mean CFB in Hb at Week 16 in the pegcetacoplan group was seen in White subjects. Asian and Black/African American subjects in the pegcetacoplan group had a mean CFB that was approximately 1 g/dL lower than for White subjects. By age, subjects in the pegcetacoplan group were comparable in mean CFB at Week 16. Meaningful subgroup comparisons were not possible for the eculizumab arm given the large number of subjects who were removed from the analysis because of transfusions.

Breakthrough haemolysis was analysed post-hoc and is of exploratory value, but of great clinical relevance. Signs of breakthrough haemolysis while LDH elevated (after prior reduction of LDH) was observed in 2 subjects (4.9%) in pegcetacoplan and 13 subjects (33.3%) in eculizumab arm. However, according to available literature data, eculizumab underperformed in this pivotal trial. According to literature, the incidence of breakthrough haemolysis with eculizumab is up to 27%, while in a recent pivotal study of ravulizumab it was as low as 5% (Kulasekararaj et al., 2019). In the present study, the

incidence of breakthrough haemolysis with eculizumab is 33.3%, which is significantly higher than in literature studies. Underperformance of the eculizumab was already commented regarding transfusion avoidance.

Finally, as mentioned in the protocol, self-administration of pegcetacoplan is permitted in section 4.2 of the SmPC. However, the risk of severe hypersensitivity reaction (including anaphylaxis) is identified as an important potential risk with this product. Thus, the patients eligible to self-administration in whom this risk can be avoided are identified in section 4.2 of the SmPC: "Self administration and home infusion should be considered for patients who have tolerated treatment well in experienced treatment centres. The decision of a possibility of self administration and home infusions should be made after evaluation and recommendation from the treating physician." Guidance is also available as part of the patient information pack (see RMP section).

Supportive clinical studies have been provided by the Applicant but not in the target population or in the claimed posology.

2.6.7. Conclusions on the clinical efficacy

Study APL2-302 is a randomized, controlled, global Phase 3 trial designed to compare the clinical efficacy of pegcetacoplan with a representative C5 inhibitor, eculizumab. The primary endpoint (CFB in Hb level) has been reached in this superiority trial. The following key secondary endpoints: transfusion avoidance, CFB in ARC level and CFB in FACIT-Fatigue score were consistent with the primary analysis. Key secondary endpoints were tested first for non-inferiority and, if all were met, then superiority was tested sequentially for transfusion avoidance, ARC, LDH, and FACIT-Fatigue score using a closed-testing procedure at a significance level of 0.05. CFB in LDH level did not meet non-inferiority by the prespecified analysis. However, a greater percentage of subjects on pegcetacoplan achieved LDH normalization, as compared with eculizumab.

When all available data are used, results are in line with the primary analyses but the magnitude of benefit observed with pegcetacoplan compared to eculizumab is smaller, albeit still statistically significant and clinically relevant.

The proposed indication as amended is in line with the studied population and reflects second-line treatment, in patients still anaemic despite being treated with a C5 inhibitor.

2.6.8. Clinical safety

The safety data for pegcetacoplan in subjects with paroxysmal nocturnal hemoglobinuria (PNH) via subcutaneous (SC) infusion are taken from 6 studies in adults. Of these, 3 studies are completed (Study APL2-202 (Study 202), Study APL2-CP-PNH-204 (Study 204) and Study APL-CP0514 (Study CP0514)) and 2 studies are ongoing (study 307 and study 308). For the pivotal Study APL2-302, the randomized control period (RCP) is completed whereas the open-label phase is ongoing.

2.6.8.1. Patient exposure

Through the data cut-off date (31 May 2020), the safety database consisted of 110 patients with PNH who received SC pegcetacoplan in the 4 studies submitted. Of the total safety database, 36 patients of 115 (31.3%) received pegcetacoplan for more than 1 year, 9 subjects (7.8%) for >2 years, and 4 subjects (3.5%) for >3 years and on the 80 patients enrolled in the pivotal study APL2-302 only 10 subjects (12.5%) received pedcetacoplan for >1 year, and no patient received pegcetacoplan for more than 2 years.

The pivotal study APL2-302 was composed by a run-in period of 28 days and by a randomized control period (RCP) of 16 weeks. In most subjects (n = 79), there was a period of combined pegcetacoplan and eculizumab exposure during the RCP, and this period is denoted as "pegcetacoplan + eculizumab".

During the run-in period, 80 subjects received both pegcetacoplan (at a dose of 1080 mg twice weekly or every 3 days) and eculizumab (at their current dosage) during this study period with a median duration of treatment of 29 days for both groups. During the RCP, 41 subjects received pegcetacoplan for a median of 110.0 days, and 39 subjects received eculizumab for a median of 99.0 days.

All subjects started pegcetacoplan at a dosage of 1080 mg subcutaneously twice weekly in the pivotal study APL2-302. The protocol required dose escalation if a subject had elevated LDH levels > 2 x ULN.

In the 3 supportive studies (Study 202, Study 204, and Study CP0514), patients received pegcetacoplan at a dose from 270mg/day to 360mg/day. In the study 202, all 4 subjects received 270mg pegcetacoplan daily for a duration of 1 year. The 20 patients of the cohort 2 of the study 204 received a starting dose of 270mg/day and then doses up to 360mg/day and the 6 patients of the cohort 4 of the study CP0514 received a dose of 270mg/day.

Demographic and Baseline Characteristics

The majority of the enrolled patients were female with 61% of female in the pivotal study and overall for the 4 studies, were young with a median age of 50.5 years old (min, max: 19, 81) in the pivotal study and 42 years old (min, max: 19, 81) overall for the 4 studies and were mostly White (53.6%) following by Asian except for the cohort 2 of study 204 where 75% of patients were Asian. In the pivotal study APL2-302, of the 80 patients enrolled 17 patients (21.3%) had more than 65 years old and among them 10 patients (10/41; 24.4%) were randomized in the pegcetacoplan group during the RCP.

Subject Disposition

Table 37: Summary of Key Safety Data for Study APL2-302, Study 202, Study 204, and Study CP0514

	Study APL2-302[a]				Study 202[b]	Study 204[b]	Study CP0514[c]
	1080 mg twice weekly SC pegcetacoplan				270 mg/day SC pegcetacoplan		
	Run-in set (run-in period)	Safety set (randomized controlled period)			Safety set		
Parameter Statistic	Pegcetacoplan + eculizumab (N = 80)	Pegcetacoplan + eculizumabd (N = 79)	Pegcetacoplan (N = 41)	Eculizumab (N = 39)	(N = 4)	Cohort 2 (N = 20)	Cohort 4 (N = 6)
All TEAEs							
n (%)	69 (86.3)	12 (15.2)	36 (87.8)	34 (87.2)	3 (75.0)	18 (90.0)	6 (100)
Total events	303	27	270	135	60	137	427
Total unique events	100	19	100	73	11	81	136
TEAEs related to pegcetacoplan[e]							
n (%)	44 (55.0)	2 (2.5)	16 (39.0)	NA	2 (50.0)	9 (45.0)	4 (66.7)
Total events	–	–	–	–	52	30	68
Unique events	–	–	–	–	6	19	18
Deaths							
n (%)	0	0	0	0	0	1 (5.0)	0

TEAEs leading to discontinuations	0	0	3 (7.3)	0	0	2 (10.0)	0
SAEs							
n (%)	1 (1.3)	2 (2.5)	7 (17.1)	6 (15.4)	1 (25.0)	6 (30.0)	2 (33.3)
Total events	1	2	8	11	1	12	8
Unique events	1	2	7	10	1	10	7
Maximum severity of all TEAEs							
n (%)							
Mild	51 (63.8)	8 (10.1)	19 (46.3)	14 (35.9)	2 (50.0)	3 (15.0)	–
Moderate	16 (20.0)	3 (3.8)	9 (22.0)	15 (38.5)	–	8 (40.0)	2 (33.3)
Severe	2 (2.5)	1 (1.3)	8 (19.5)	5 (12.8)	1 (25.0)	6 (30.0)[f]	4 (66.7)

Abbreviations: N = number of subjects in each group or population; n = number of subjects in each category; NA = not applicable; SAE = serious adverse event; SC = subcutaneous; TEAE = treatment-emergent adverse event.
[a] Study duration was 16 weeks. Dosage could be increased to 1080 mg every 3 days if clinically indicated.
[b] Study duration was up to 365 days. Dosage could be increased to 360 mg/day if clinically indicated. Subjects were naive to C5 inhibitor treatment.
[c] Study duration was 2 years. Dosage could be increased to 360 mg/day if clinically indicated. Subjects remained anemic despite treatment with eculizumab.
[d] Treatment-emergent adverse events that occurred after the randomization date but before the first monotherapy were summarized under the pegcetacoplan + eculizumab group.
[e] Includes events that were deemed at least possibly related to pegcetacoplan by the investigator.
[f] Includes 1 life-threatening event that was classified separately
Note: A dash signifies that the parameter or statistic was not determined in this study.
Soucres: Study APL2-302, Table 14.3.1.1.1; Table 14.3.1.1.2. Study 202, Table 14.3.1.1. Study 204, Table 14.3.1.1. Study CP0514,

2.6.8.2. Adverse events

Run-in period of the pivotal study APL2-302

During the run-in period, 80 patients received the combination of pegcetacoplan and eculizumab. Of the 80 patients 69 subjects (86.3%) experienced at least 1 TEAE with the majority were of a maximum severity of mild (51 patients [63.8%]), followed by moderate for 16 patients (20.0%) and severe for 2 patients (2.5%) (Sepsis and neutropenia). There were no TEAEs leading to death, study discontinuation, or study drug discontinuation during this period.

The most common AEs were reported in the SOC general disorders and administration site conditions (49 subjects [61.3%]) with injection site reactions reported in 46 subjects (57.5%) including injection site erythema, pruritus and swelling as the most common events. However, none injection site reactions were severe, serious, or led to study drug discontinuation.

AEs that were next more often reported were gastrointestinal disorders (16 subjects [20.0%]) including diarrhoea (6 subjects [7.5%]) and nausea (5 subjects [6.3%]) and nervous system disorders (14 subjects [17.5%]) with headache being the most common events (10 subjects [12.5%]).

Infections and infestations were reported in 11 subjects (13.8%) with one was of moderate maximum severity (otitis externa) and one was severe (sepsis).

More TEAEs were considered to be related to pegcetacoplan (44/80; 55.0%) or to the infusion (32/80; 40%), than to eculizumab (4/80; 5.0%).

There were no TEAEs leading to death, study discontinuation, or study drug discontinuation during the run-in period.

TEAEs in 44 subjects (55.0%) were deemed to be related to pegcetacoplan. General disorders and administration site conditions were reported as event counted as pegcetacoplan-related by 37 subjects (46.3%). Injection site erythema was the most frequently reported of these events (23 subjects [28.8%]), followed by injection site pruritus and injection site swelling (8 subjects [10% each]) but also injection site reaction, injection site induration and injection site pain. Six subjects (7.5%) reported nervous system disorders, including headache reported by 4 subjects (5%). No other TEAEs were reported in 5% or more of subjects in this study period.

During the run-in period 4 subjects (5%) reported eculizumab-related TEAEs including 1 report each of ALT increased, platelet count decreased, leukopenia, neutropenia, sepsis, and pain in jaw. Events considered related to both pegcetacoplan and eculizumab included ALT increased, platelet count decreased, leukopenia, neutropenia and sepsis.

Randomized controlled period (RCP) of the pivotal study

- Pegcetacoplan + Eculizumab after randomization but before monotherapy dosing began

During the RCP, the majority of subjects (79 of 80) started monotherapy after Day 2 to fit their dosing schedule. Twelve (15.2%) of these subjects (noted in the pegcetacoplan + eculizumab Group column in Table 44) reported at least 1 TEAE after randomization but before monotherapy dosing began. TEAEs reported in more than 2 subjects included fatigue and pyrexia (3 subjects each, 3.8%) and viral upper respiratory tract infection (URTI), viral infection, dizziness, and chromaturia (2 subjects each, 2.5%). The remaining TEAEs were reported by only 1 subject each.

Twelve subjects (15.2%) who received pegcetacoplan + eculizumab experienced 27 TEAEs (19 unique events). Two of these were deemed related to pegcetacoplan and 1 was considered related to eculizumab. Eight subjects (10.1%) reported TEAEs with a maximum severity of mild; 3 subjects (3.8%) reported a TEAE with a maximum severity of moderate; and 1 subject reported an event with a maximum severity of severe. No TEAEs led to study drug discontinuation. Two subjects reported 2 unique SAEs. Neither SAE was deemed related to either study drug.

- Monotherapy

After the beginning of the monotherapy during the RCP, a similar percentage of subjects in both treatment groups reported at least 1 TEAE, 36 patients (87.8%) in the pegcetacoplan group and 34 patients (87.2%) in the eculizumab group.

Table 38: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term During Randomized Controlled Period (Safety Set)

System Organ Class/ Preferred Term	Pegcetacoplan + eculizumab * (N=79) n (%)	Pegcetacoplan (N=41) n (%)	Eculizumab (N=39) n (%)
Any TEAEs	12 (15.2)	36 (87.8)	34 (87.2)
General disorders and administration site	5 (6.3)	22 (53.7)	14 (35.9)
Injection site erythema	0	7 (17.1)	0
Injection site reaction	0	5 (12.2)	0
Injection site swelling	0	4 (9.8)	0
Asthenia	0	3 (7.3)	3 (7.7)
Injection site induration	0	3 (7.3)	0
Fatigue	3 (3.8)	2 (4.9)	6 (15.4)

Injection site bruising	0	2 (4.9)	0
Pyrexia	3 (3.8)	2 (4.9)	2 (5.1)
Chest discomfort	0	1 (2.4)	0
Chest pain	0	1 (2.4)	1 (2.6)
Influenza like illness	0	1 (2.4)	0
Infusion site swelling	0	1 (2.4)	0
Injection site pain	0	1 (2.4)	0
Injection site pruritus	0	1 (2.4)	0
Non-cardiac chest pain	0	1 (2.4)	0
Pain	0	1 (2.4)	1 (2.6)
Peripheral swelling	0	1 (2.4)	0
Tenderness	0	1 (2.4)	0
Vaccination site reaction	0	1 (2.4)	0
Hyperthermia	0	0	1 (2.6)
Oedema	0	0	1 (2.6)
Vaccination site pain	0	0	2 (5.1)
Musculoskeletal and connective tissue disorders	2 (2.5)	16 (39.0)	7 (17.9)
Back pain	1 (1.3)	3 (7.3)	4 (10.3)
Pain in extremity	0	3 (7.3)	1 (2.6)
Arthralgia	0	2 (4.9)	1 (2.6)
Neck pain	0	2 (4.9)	0
Bone pain	0	1 (2.4)	0
Joint swelling	0	1 (2.4)	0
Muscle spasms	0	1 (2.4)	0
Musculoskeletal pain	0	1 (2.4)	0
Myalgia	1 (1.3)	1 (2.4)	1 (2.6)
Sacroiliitis	0	1 (2.4)	0
Gastrointestinal disorders	2 (2.5)	15 (36.6)	9 (23.1)
Diarrhoea	1 (1.3)	9 (22.0)	1 (2.6)
Abdominal pain	0	5 (12.2)	4 (10.3)
Abdominal pain upper	0	2 (4.9)	0
Nausea	0	2 (4.9)	2 (5.1)
Abdominal discomfort	0	1 (2.4)	0
Dental caries	0	1 (2.4)	0
Dyspepsia	0	1 (2.4)	0
Gastric ulcer	0	1 (2.4)	0
Swollen tongue	0	1 (2.4)	0
Abdominal distension	0	0	1 (2.6)
Abdominal pain lower	1 (1.3)	0	0
Constipation	0	0	1 (2.6)
Epigastric discomfort	0	0	1 (2.6)
Vomiting	0	0	3 (7.7)

Infections and infestations	4 (5.1)	12 (29.3)	10 (25.6)
Oral herpes	0	2 (4.9)	0
Viral upper respiratory tract infection	2 (2.5)	2 (4.9)	2 (5.1)
Bacterial infection	0	1 (2.4)	0
Fungal infection	0	1 (2.4)	0
Gastroenteritis	0	1 (2.4)	1 (2.6)
Gastrointestinal infection	0	1 (2.4)	0
Gastrointestinal viral infection	0	1 (2.4)	0
Nasopharyngitis	0	1 (2.4)	0
Periodontitis	0	1 (2.4)	0
Pulpitis dental	0	1 (2.4)	0
Rhinitis	0	1 (2.4)	0
Tonsillitis	0	1 (2.4)	0
Tonsillitis bacterial	0	1 (2.4)	0
Upper respiratory tract infection	0	1 (2.4)	1 (2.6)
Vulvovaginal mycotic infection	0	1 (2.4)	0
Bronchitis	0	0	1 (2.6)
Ear infection	0	0	1 (2.6)
Respiratory tract infection	0	0	1 (2.6)
Rhinovirus infection	0	0	1 (2.6)
Sinusitis	0	0	1 (2.6)
Urinary tract infection	0	0	2 (5.1)
Viral infection	2 (2.5)	0	0
Blood and lymphatic system disorders	1 (1.3)	7 (17.1)	16 (41.0)
Haemolysis	0	4 (9.8)	9 (23.1)
Thrombocytopenia	0	2 (4.9)	0
Eosinophilia	0	1 (2.4)	0
Anaemia	0	0	5 (12.8)
Extravascular haemolysis	0	0	1 (2.6)
Haemolytic anaemia	1 (1.3)	0	1 (2.6)
Injury, poisoning and procedural complications	1 (1.3)	6 (14.6)	1 (2.6)
Ankle fracture	0	1 (2.4)	0
Cartilage injury	0	1 (2.4)	0
Contusion	0	1 (2.4)	0
Limb injury	0	1 (2.4)	0
Tooth fracture	0	1 (2.4)	0
Traumatic haematoma	0	1 (2.4)	0
Vaccination complication	1 (1.3)	1 (2.4)	0
Fall	0	0	1 (2.6)
Nervous system disorders	3 (3.8)	6 (14.6)	12 (30.8)
Headache	1 (1.3)	3 (7.3)	9 (23.1)
Dizziness	2 (2.5)	1 (2.4)	4 (10.3)

Facial paralysis	0	1 (2.4)	0
Paraesthesia	0	1 (2.4)	1 (2.6)
Syncope	0	1 (2.4)	0
Complex regional pain syndrome	0	0	1 (2.6)
Disturbance in attention	1 (1.3)	0	0
Lethargy	1 (1.3)	0	1 (2.6)
Peripheral sensory neuropathy	0	0	1 (2.6)
Vascular disorders	0	5 (12.2)	2 (5.1)
Hypertension	0	3 (7.3)	1 (2.6)
Haematoma	0	1 (2.4)	0
Orthostatic hypotension	0	1 (2.4)	0
Peripheral arterial occlusive disease	0	0	1 (2.6)
Skin and subcutaneous tissue disorders	1 (1.3)	4 (9.8)	2 (5.1)
Erythema	0	2 (4.9)	0
Pigmentation disorder	0	1 (2.4)	0
Skin disorder	0	1 (2.4)	0
Hyperhidrosis	0	0	1 (2.6)
Pruritus	0	0	1 (2.6)
Rash	1 (1.3)	0	0
Investigations	0	3 (7.3)	2 (5.1)
Bilirubin conjugated increased	0	1 (2.4)	0
Blood creatinine increased	0	1 (2.4)	0
Weight increased	0	1 (2.4)	0
Body temperature increased	0	0	1 (2.6)
Platelet count decreased	0	0	1 (2.6)
Metabolism and nutrition disorders	0	3 (7.3)	4 (10.3)
Gout	0	1 (2.4)	0
Hypercalcaemia	0	1 (2.4)	0
Vitamin B12 deficiency	0	1 (2.4)	0
Decreased appetite	0	0	2 (5.1)
Hypocalcaemia	0	0	1 (2.6)
Hypokalaemia	0	0	1 (2.6)
Iron overload	0	0	1 (2.6)
Respiratory, thoracic and mediastinal disorders	0	3 (7.3)	6 (15.4)
Cough	0	1 (2.4)	0
Dyspnoea	0	1 (2.4)	2 (5.1)
Dyspnoea exertional	0	1 (2.4)	1 (2.6)
Epistaxis	0	1 (2.4)	0
Lung disorder	0	1 (2.4)	0
Rhinalgia	0	1 (2.4)	0
Nasal congestion	0	0	1 (2.6)
Oropharyngeal pain	0	0	2 (5.1)

Productive cough	0	0	1 (2.6)
Eye disorders	0	2 (4.9)	0
Dry eye	0	1 (2.4)	0
Eye swelling	0	1 (2.4)	0
Hepatobiliary disorders	0	2 (4.9)	4 (10.3)
Cholelithiasis	0	1 (2.4)	0
Ocular icterus	0	1 (2.4)	1 (2.6)
Biliary colic	0	0	1 (2.6)
Hepatitis	0	0	1 (2.6)
Hepatocellular injury	0	0	1 (2.6)
Hyperbilirubinaemia	0	0	2 (5.1)
Jaundice	0	0	1 (2.6)
Psychiatric disorders	1 (1.3)	2 (4.9)	5 (12.8)
Anxiety	0	1 (2.4)	2 (5.1)
Depressed mood	0	1 (2.4)	0
Restlessness	0	1 (2.4)	0
Depression	0	0	1 (2.6)
Insomnia	0	0	2 (5.1)
Irritability	0	0	1 (2.6)
Mental disorder	0	0	1 (2.6)
Sleep disorder	1 (1.3)	0	0
Reproductive system and breast disorders	1 (1.3)	2 (4.9)	0
Breast pain	0	1 (2.4)	0
Menopausal symptoms	0	1 (2.4)	0
Vaginal discharge	1 (1.3)	0	0
Cardiac disorders	1 (1.3)	1 (2.4)	2 (5.1)
Atrial fibrillation	0	1 (2.4)	0
Pericardial effusion	0	1 (2.4)	0
Tachycardia	0	1 (2.4)	0
Angina pectoris	1 (1.3)	0	0
Palpitations	0	0	2 (5.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (2.4)	0
Basal cell carcinoma	0	1 (2.4)	0
Renal and urinary disorders	2 (2.5)	1 (2.4)	7 (17.9)
Haematuria	0	1 (2.4)	1 (2.6)
Chromaturia	2 (2.5)	0	2 (5.1)
Haemoglobinuria	0	0	1 (2.6)
Nephrolithiasis	0	0	1 (2.6)
Renal pain	0	0	1 (2.6)
Urinary tract disorder	0	0	1 (2.6)
Ear and labyrinth disorders	0	0	1 (2.6)

Tinnitus	0	0	1 (2.6)

- Note: A treatment-emergent adverse event (TEAE) is an adverse event that commenced on or after the time of first study drug administration or an adverse event with increase in severity from pretreatment. Adverse events were coded to system organ class and preferred term using MedDRA Version 20.0.
- If a subject has multiple occurrences of a TEAE, the subject is presented only once in the subject count (n) column for a given system organ class and Preferred Term.
- * TEAEs that occurred after randomization date but before the first monotherapy are summarized under the pegcetacoplan + eculizumag Group.
- Source: Table 14.3.1.2.2

Sixteen subjects (39%) in the pegcetacoplan group and 7 subjects (17.9%) in the eculizumab group reported a **drug-related** TEAE, largely accounted for by injection/infusion site reactions, which were reported solely in the pegcetacoplan group. Other than ISRs, there were no other drug-related TEAEs occurring in 5% or more of one group as compared to the other.

2.6.8.3. Serious adverse event/deaths/other significant events

One serious TEAE of sepsis occurred during the run-in period. This event was considered related to both pegcetacoplan and eculizumab. The subject recovered without discontinuation of both pegcetacoplan and eculizumab. The subject had no further SAEs or TEAEs of infection.

A similar proportion of subjects in the pegcetacoplan and eculizumab groups experienced **SAEs** during the RCP: 7 subjects (17.1%) in the pegcetacoplan group experienced 8 SAEs, and 6 subjects (15.4 %) in the eculizumab group experienced 11 SAEs.

Table 39: Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term During Randomized Controlled Period (Safety Set)

System organ class/ preferred term	Statistics	Pegcetacoplan + eculizumab* (N=39)	Pegcetacoplan (N=41)	Eculizumab (N=39)
Any Serious TEAEs	n (%)	2 (2.5)	7 (17.1)	6 (15.4)
Blood and lymphatic system disorders	n (%)	1 (1.3)	2 (4.9)	4 (10.3)
Haemolysis	n (%)	0	2 (4.9)	1 (2.6)
Anaemia	n (%)	0	0	2 (5.1)
Haemolytic anaemia	n (%)	1 (1.3)	0	1 (2.6)
Infections and infestations	n (%)	1 (1.3)	2 (4.9)	0
Bacterial infection	n (%)	0	1 (2.4)	0
Gastroenteritis	n (%)	0	1 (2.4)	0
Viral upper respiratory tract infection	n (%)	1 (1.3)	0	0
Cardiac disorders	n (%)	0	1 (2.4)	0
Atrial fibrillation	n (%)	0	1 (2.4)	0
General disorders and administration site conditions	n (%)	0	1 (2.4)	2 (5.1)
Pyrexia	n (%)	0	1 (2.4)	1 (2.6)
Hyperthermia	n (%)	0	0	1 (2.6)
Nervous system disorders	n (%)	0	1 (2.4)	0
Facial paralysis	n (%)	0	1 (2.4)	0
Respiratory, thoracic and mediastinal disorders	n (%)	0	1 (2.4)	0
Dyspnoea	n (%)	0	1 (2.4)	0

Gastrointestinal disorders	n (%)	0	0	1 (2.6)
Abdominal pain	n (%)	0	0	1 (2.6)
Hepatobiliary disorders	n (%)	0	0	1 (2.6)
Biliary colic	n (%)	0	0	1 (2.6)
Hepatocellular injury	n (%)	0	0	1 (2.6)
Hyperbilirubinaemia	n (%)	0	0	1 (2.6)
Jaundice	n (%)	0	0	1 (2.6)

Note: A treatment-emergent adverse event (TEAE) is an adverse event that commenced on or after the time of first
study drug administration or an adverse event with increase in severity from pretreatment.
Adverse events were coded to system organ class and preferred term using MedDRA Version 20.0.
If a subject has multiple occurrences of a TEAE, the subject is presented only once in the subject count (n) column for a given system organ class and Preferred Term.
* TEAEs that occurred after randomization date but before the first monotherapy are summarized under the pegcetacoplan + eculizumab Group.
Source: Table 14.3.1.6.2

During the RCP, one SAE (2.4%) of facial paralysis in the pegcetacoplan group was considered related to pegcetacoplan, and one SAE (2.6%) of pyrexia in the eculizumab group was considered related to eculizumab.

No **death** occurred in the pivotal study APL2-302 before Week 16. However, a fatal SAE of COVID-19 that was deemed not related to pegcetacoplan by the investigator was reported in the open-label phase (OLP) of the study APL2-302 that occurred after Week 16 (see section below with updated safety data from the OLP).

Among the 3 supportive studies, no death occurred in the study 202 but 3 deaths occurred in the Study 204 and CP0514, 2 of which were on-study (aplastic anaemia in the cohort 2 of the study 204 and intracranial haemorrhage in the cohort 1 of the study CP0514) whereas the last one was not on study (abdominal neoplasm in the cohort 2 of the study 204) and none of which were deemed related to pegcetacoplan by the investigator.

2.6.8.4. Laboratory findings

Overall, the laboratory findings including haematology and chemistry were consistent with those expected in patients with PNH, and changes in these parameters were consistent with the efficacy findings that pegcetacoplan improves haemolytic anaemia associated with PNH.

2.6.8.5. Safety in special populations

One study in subjects with renal impairment, Study 205, has been performed. Pegcetacoplan was well tolerated across both the severe renal impairment and control cohorts with no major differences between cohorts other than ongoing TEAEs and concomitant medications reflective of the underlying medical condition and not pegcetacoplan treatment.

No formal studies of pegcetacoplan in pregnant women have been performed up to the data cut-off date (31 May 2020), and contraception is required for women of childbearing potential participating in clinical studies with pegcetacoplan.

There is no experience with pegcetacoplan in women who are breastfeeding.

There are no reports of pegcetacoplan overdosage in clinical studies, and there is unlikely to be a misuse problem with pegcetacoplan because it does not affect the central nervous system.

The Applicant has no information at this time regarding any effects of pegcetacoplan on those to whom it is administered related to their ability to drive or operate machinery or to any impairment of mental ability. The results of the nonclinical pharmacology studies do not suggest a depressive central nervous system effect.

The pivotal Study APL2-302 did not include children or adolescents.

Table 40: Summary of treatment-emergent adverse events by age and preferred term (studies APL2-302, 202, 204 and CP0514)

MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+ number (percentage)
	Pegcetacoplan N=64	Pegcetacoplan N=9	Pegcetacoplan N=3	Pegcetacoplan N=0
Total AEs	891	37	15	0
Serious AEs – Total	29	1	0	0
- Fatal	1 (1.6)	0	0	0
- Hospitalization	16 (25.0)	1 (11.1)	0	0
- Life-threatening	2 (3.1)	0	0	0
- Disability/incapacity	0	0	0	0
- Other (medically significant)	1 (1.6)	0	0	0
AE leading to drop-out	5 (7.8)	1 (11.1)	0	0
Psychiatric disorders	3 (4.7)	1 (11.1)	0	0
Nervous system disorders	16 (25.0)	2 (22.2)	0	0
Accidents and injuries	11 (17.2)	2 (22.2)	0	0
Cardiac disorders	2 (3.1)	0	0	0
Vascular disorders	6 (9.4)	2 (22.2)	0	0
Cerebrovascular disorders	0	0	0	0
Infections and infestations	24 (37.5)	2 (22.2)	1 (33.3)	0
Anticholinergic syndrome	12 (18.8)	3 (33.3)	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	8 (12.5)	1 (11.1)	0	0
Other AE appearing more frequently in older subjects[a]	31 (48.4)	6 (66.7)	2 (66.7)	0

Data from studies APL2-302, 202, 204 and CP0514
[a] Includes TEAEs with higher percentage of occurrence in subjects 65 years of age and older compared to subjects under 65 years of age.

2.6.8.6. Immunological events

In the pivotal study a low incidence of anti-pegcetacoplan peptide antibody response (2 of 80 subjects [2.5%]) was observed whereas higher percentages of anti-PEG antibody response were detected. This anti-PEG antibody response is due to preexisting anti-PEG antibodies (66 of 80 subjects [82.5%]) which could be explained by the development of anti-PEG antibodies after prior exposure to PEG-containing products including many medicines, cosmetics, and food products. However, the neutralizing antibody

analysis is ongoing and not provided in this application. In the pivotal study, the incidence of treatment-emergent or treatment-boosted anti-PEG response was low (one for each case [1.3%]). The treatment-boosted anti-PEG response observed was considered transient. Titer values associated with the positive anti-pegcetacoplan peptide antibody response, treatment-emergent anti-PEG response, and treatment-boosted anti-PEG response were all considered low (less than 1:40).

Overall immunogenicity are consistent across all clinical studies with infrequent and generally transient anti–pegcetacoplan peptide antibody responses detected in pegcetacoplan-treated subjects, a high percentage of preexisting anti-PEG antibody responses reported in the predose samples and a low incidences of treatment-emergent or treatment-boosted anti-PEG antibody response, with many of those responses that were transient.

However, results related to immunogenicity in the pivotal Study APL2-302 are immature.
Immunogenicity has been added as an important potential risk in the EU RMP and has been included as a safety concern to be monitored in the PASS

2.6.8.7. Discontinuation due to adverse events

No TEAEs leading to discontinuation of study drug or withdrawal from the study were reported during the run-in period.

During the RCP, 3 subjects (7.3%) **discontinued** because of TEAEs, all in the pegcetacoplan group, and all because of breakthrough haemolysis.

Updated safety data from the Open-label phase portion of Study APL2-302

Further safety data from the OLP (Open-label phase) portion of Study APL2-302 showing safety data at 48-week (data cutoff date of 23 September 2020) was provided during the procedure.

Table 41: Subject Disposition During the Open-Label Period (ITT Set)

RCP treatment		**Eculizumab**		**Pegcetacopl**	
OLP treatment schedule		**Crossover to pegcetacoplan**		**Continue pegcetacoplan**	**Total pegcetacoplan**
Actual OLP treatment		**Pegcetacoplan +**	**Pegcetacoplan monotherapy**	**Pegcetacoplan monotherapy**	**Pegcetacoplan monotherapy**
Received ⩾1 dose study drug	n (%)	39 (100)	39 (100)	38 (100)	77 (100)
Completed study treatment	n (%)	NA	32 (82.1)	35 (92.1)	67 (87.0)
Withdrawn from study treatment	n (%)	0	7 (17.9)	3 (7.9)	10 (13.0)
Primary reason for treatment	n (%)				
AE	n (%)	0	7 (17.9)	2 (5.3)	9 (11.7)
Physician decision	n (%)	0	0	1 (2.6)	1 (1.3)
Completed study	n (%)	0	32 (82.1)	35 (92.1)	67 (87.0)
Completed pre–COVID-19	n (%)	0	8 (20.5)	7 (18.4)	15 (19.5)
Completed post–COVID-19	n (%)	0	24 (61.5)	28 (73.7)	52 (67.5)
Withdrawn from study	n (%)	0	7 (17.9)	3 (7.9)	10 (13.0)
Primary reason for withdrawal	n (%)				
AE	n (%)	0	7 (17.9)	3 (7.9)	10 (13.0)

RCP treatment		Eculizumab		Pegcetacopl	
OLP treatment schedule		Crossover to pegcetacoplan		Continue pegcetacoplan	Total pegcetacoplan
Actual OLP treatment		Pegcetacoplan +	Pegcetacoplan monotherapy	Pegcetacoplan monotherapy	Pegcetacoplan monotherapy
Entered the extension study (Study APL2-307)	n (%)	NA	32 (82.1)	32 (82.4)	64 (83.1)

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; ITT = intent-to-treat; N = number of subjects in each group; n = number of subjects in the sample; NA = not applicable; OLP = Open-Label Period; RCP = Randomised Controlled Period; W = week; WHO = World Health Organization.

Notes: Completed study is defined as either subject completed study or roller over to extension study.
"Post–COVID-19" is defined as on or after 11 March 2020 (the date the WHO declared COVID-19 a pandemic).

Source: Table 14.1.2.4.

Table 42: Overview of Treatment-Emergent Adverse Events During the Open-Label and Follow-Up Periods (Safety Set)

RCP treatment		Eculizumab		Pegcetacoplan	
OLP treatment schedule		Crossover to pegcetacoplan		Continue pegcetacoplan	Total pegcetacoplan
Actual OLP treatment		Pegcetacoplan + eculizumab N = 35	Pegcetacoplan monotherapy N = 39	Pegcetacoplan monotherapy N = 38	Pegcetacoplan monotherapy N = 77
	Statistics				
Any TEAEs	n (%)	19 (54.3)	37 (94.9)	33 (86.8)	70 (90.9)
Total events	n	55	322	354	676
Total unique events	n	32	139	114	205
TEAEs by relationship to pegcetacoplan					
Related	n (%)	11 (31.4)	18 (46.2)	15 (39.5)	33 (42.9)
Unrelated	n (%)	8 (22.9)	19 (48.7)	18 (47.4)	37 (48.1)
TEAEs by relationship to eculizumab					
Related	n (%)	0	NA	NA	NA
Unrelated	n (%)	19 (54.3)	NA	NA	NA
TEAEs by relationship to infusion					
Related	n (%)	6 (17.1)	8 (20.5)	4 (10.5)	12 (15.6)
Unrelated	n (%)	13 (37.1)	29 (74.4)	29 (76.3)	58 (75.3)
Serious TEAEs		1 (2.9)	10 (25.6)	8 (21.1)	18 (23.4)
Total events		1	13	16	29
Total unique events		1	10	15	24
Serious TEAEs by relationship to pegcetacoplan	n (%)				
Related	n	0	3 (7.7)	1 (2.6)	4 (5.2)
Unrelated	n	1 (2.9)	7 (17.9)	7 (18.4)	14 (18.2)
Serious TEAEs by relationship to eculizumab					

RCP treatment		Eculizumab		Pegcetacoplan	
OLP treatment schedule		Crossover to pegcetacoplan		Continue pegcetacoplan	Total pegcetacoplan
Actual OLP treatment		Pegcetacoplan + eculizumab N = 35	Pegcetacoplan monotherapy N = 39	Pegcetacoplan monotherapy N = 38	Pegcetacoplan monotherapy N = 77
	Statistics				
Related	n (%)	0	NA	NA	NA
Unrelated	n (%)	1 (2.9)	NA	NA	NA
Serious TEAEs by relationship to infusion					
Related	n (%)	0	0	0	0
Unrelated	n (%)	1 (2.9)	10 (25.6)	8 (21.1)	18 (23.4)
TEAEs by maximum severity					
Mild	n (%)	13 (37.1)	16 (41.0)	17 (44.7)	33 (42.9)
Moderate	n (%)	4 (11.4)	12 (30.8)	8 (21.1)	20 (26.0)
Severe	n (%)	2 (5.7)	9 (23.1)	8 (21.1)	17 (22.1)
Injection site reaction	n (%)	6 (17.1)	11 (28.2)	7 (18.4)	18 (23.4)
TEAEs leading to study discontinuation	n (%)	0	6 (15.4)	2 (5.3)	8 (10.4)
TEAEs leading to death	n (%)	0	0	1 (2.6)	1 (1.3)
TEAEs due to COVID-19	n (%)	0	0	1 (2.6)	1 (1.3)
TEAEs beyond Week 48	n (%)	0	2 (5.1)	1 (2.6)	3 (3.9)

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; N = not applicable; N = number of subjects in each group; n = number of subjects in each category; OLP = Open-Label Period; PT = Preferred Term; RCP = Randomised Controlled Period; TEAE = treatment-emergent adverse event.
Notes: AEs were coded to SOC and PT using MedDRA Version 23.0.
An AE (classified by PT) that occurred during the study was considered a TEAE if it had a start date on or after the first dose of investigational product or if it had a start date before the first dose but increased in severity on or after the date of the first dose. It applied up to 30 days follow-up. If a subject had multiple occurrences of a TEAE, the subject was presented only once in the subject count and all occurrences are counted each time in the total events count. Unique events count is the number of unique preferred terms. Definitely related and possibly related AEs were classified as related AEs while unlikely related and not related AEs were classified as unrelated AEs. AEs with unknown relationship to study drug were counted as related AE in the table.
Source: Table 14.3.1.1.3.

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each group; n = number of subjects in each category; OLP = Open-Label Period; PT = Preferred Term; RCP = Randomised Controlled Period; SOC = System Organ Class; TEAE = treatment-emergent adverse event.
Notes: AEs were coded to SOC and PT using MedDRA Version 23.0.
An AE (classified by PT) that occurred during the study was considered a TEAE if it had a start date on or after the first dose of investigational product or if it had a start date before the first dose but increased in severity on or after the date of the first dose. It applied up to 30 days follow-up. If a subject had multiple occurrences of a TEAE, the subject was presented only once in the subject count (n) column for a given SOC and PT.
Source: Table 14.3.1.6.3.

Table 43: Treatment-Emergent Adverse Events Reported by During the Open-in Any Treatment Group by System Organ Class and Preferred Term During the Open-Label and Follow-Up Periods (Safety Set)

RCP treatment		Eculizumab		Pegcetacopla	
OLP treatment schedule		Crossover to pegcetacoplan		Continue pegcetaco plan	Total pegcetaco plan
Actual OLP treatment		Pegcetacopl an + eculizumab	Pegcetaco plan monothera	Pegcetaco plan monothera	Pegcetaco plan monothera

SOC/PT	Statisti				
Any TEAEs	n (%) [e]	**19 (54.3)**	**37 (94.9), [*176.9*]**	**33 (86.8), [*139.1*]**	**70 (90.9), [*156.8*]**
Blood and lymphatic system disorders	n (%) [e]	**1 (2.9)**	**16 (41.0), [*76.5*]**	**11 (28.9), [*46.4*]**	**27 (35.1), [60.5]**
Haemolysis	n (%)	–	8 (20.5),	7 (18.4),	15 (19.5),
Neutropenia	n (%)	1 (2.9)	2 (5.1), [*9.6*]	–	2 (2.6), [*4.5*]
Thrombocytopenia	n (%)	–	3 (7.7), [*14.3*]	1 (2.6), [*4.2*]	4 (5.2), [*9.0*]
Cardiac disorders	n (%) [e]	**1 (2.9)**	**3 (7.7), [*14.3*]**	**2 (5.3), [*8.4*]**	**5 (6.5), [*11.2*]**
Angina pectoris	n (%)	–	–	2 (5.3), [*8.4*]	2 (2.6), [*4.5*]
Ear and labyrinth disorders	n (%) [e]	**–**	**3 (7.7), [*14.3*]**	**–**	**3 (3.9), [*6.7*]**
Ear discomfort	n (%)	–	2 (5.1), [*9.6*]	–	2 (2.6), [*4.5*]
Vertigo	n (%)	–	2 (5.1), [*9.6*]	–	2 (2.6), [*4.5*]
Gastrointestinal disorders	n (%) [e]	**5 (14.3)**	**14 (35.9), [*66.9*]**	**11 (28.9), [*46.4*]**	**25 (32.5), [*56.0*]**
Abdominal distension	n (%)	–	1 (2.6), [*4.8*]	3 (7.9), [*12.6*]	4 (5.2), [*9.0*]
Abdominal pain	n (%)	1 (2.9)	1 (2.6), [*4.8*]	3 (7.9), [*12.6*]	4 (5.2), [*9.0*]
Diarrhoea	n (%)	3 (8.6)	5 (12.8),	5 (13.2),	10 (13.0),
Gastrointestinal	n (%)	–	–	2 (5.3), [*8.4*]	2 (2.6), [*4.5*]
Nausea	n (%)	3 (8.6)	1 (2.6), [*4.8*]	1 (2.6), [*4.2*]	2 (2.6), [*4.5*]
Vomiting	n (%)	1 (2.9)	2 (5.1), [*9.6*]	1 (2.6), [*4.2*]	3 (3.9), [*6.7*]
General disorders and administration site conditions	n (%) [e]	**8 (22.9)**	**22 (56.4), [*105.2*]**	**15 (39.5), [*63.2*]**	**37 (48.1), [*82.9*]**
Asthenia	n (%)	–	–	3 (7.9), [*12.6*]	3 (3.9), [*6.7*]
Fatigue	n (%)	–	7 (17.9),	1 (2.6), [*4.2*]	8 (10.4),

RCP treatment		**Eculizumab**		**Pegcetacopla**	
OLP treatment schedule		**Crossover to**		**Continue pegcetaco**	**Total pegcetaco**
Actual OLP treatment		**Pegcetacopl an + eculizumab**	**Pegcetaco plan monothera**	**Pegcetaco plan monothera**	**Pegcetaco plan monothera**
SOC/PT	**Statisti**				
Hyperthermia	n (%)	–	–	2 (5.3), [*8.4*]	2 (2.6), [*4.5*]
Injection site bruising	n (%) [e]	–	2 (5.1), [*9.6*]	1 (2.6), [*4.2*]	3 (3.9), [*6.7*]
Injection site erythema	n (%) [e]	7 (20.0)	6 (15.4), [*28.7*]	3 (7.9), [*12.6*]	9 (11.7), [*20.2*]
Injection site haemorrhage	n (%)	–	3 (7.7), [*14.3*]	–	3 (3.9), [*6.7*]
Injection site induration	n (%) [e]	1 (2.9)	2 (5.1), [*9.6*]	3 (7.9), [*12.6*]	5 (6.5), [*11.2*]
Injection site pain	n (%)	–	2 (5.1), [*9.6*]	2 (5.3), [*8.4*]	4 (5.2), [*9.0*]
Injection site pruritus	n (%) [e]	1 (2.9)	4 (10.3), [*19.1*]	1 (2.6), [*4.2*]	5 (6.5), [*11.2*]
Oedema	n (%)	–	2 (5.1), [*9.6*]	1 (2.6), [*4.2*]	3 (3.9), [*6.7*]

Pain	n (%)	–	1 (2.6), [*4.8*]	2 (5.3), [*8.4*]	3 (3.9), [*6.7*]
Pyrexia	n (%)	–	3 (7.7), [*14.3*]	3 (7.9), [*12.6*]	6 (7.8),
Hepatobiliary disorders	n (%) [e]	**1 (2.9)**	**2 (5.1), [*9.6*]**	**3 (7.9), [*12.6*]**	**5 (6.5), [*11.2*]**
Hyperbilirubinaemia	n (%)	–	–	3 (7.9), [*12.6*]	3 (3.9), [*6.7*]
Immune system disorders	n (%) [e]	**1 (2.9)**	**1 (2.6), [*4.8*]**	**2 (5.3), [*8.4*]**	**3 (3.9), [*6.7*]**
Infections and infestations	n (%) [e]	**4 (11.4)**	**21 (53.8), [*100.4*]**	**21 (55.3), [*88.5*]**	**42 (54.5), [*94.1*]**
Gastroenteritis	n (%)	–	2 (5.1), [*9.6*]	1 (2.6), [*4.2*]	3 (3.9), [*6.7*]
Nasopharyngitis	n (%) [e]	1 (2.9)	6 (15.4), [*28.7*]	6 (15.8), [*25.3*]	12 (15.6), [*26.9*]
Oral herpes	n (%) [e]	–	1 (2.6), [*4.8*]	4 (10.5), [*16.9*]	5 (6.5), [*11.2*]
Rhinitis	n (%)	–	2 (5.1), [*9.6*]	–	2 (2.6), [*4.5*]
Sinusitis	n (%)	–	1 (2.6), [*4.8*]	2 (5.3), [*8.4*]	3 (3.9), [*6.7*]
Upper respiratory tract infection	n (%) [e]	–	3 (7.7), [*14.3*]	5 (13.2), [*21.1*]	8 (10.4), [*17.9*]
Urinary tract infection	n (%) [e]	–	3 (7.7), [*14.3*]	4 (10.5), [*16.9*]	7 (9.1), [*15.7*]
Injury, poisoning, and procedural complications	n (%) [e]	**2 (5.7)**	**7 (17.9), [*33.5*]**	**3 (7.9), [*12.6*]**	**10 (13.0), [*22.4*]**
Contusion	n (%)	1 (2.9)	3 (7.7), [*14.3*]	1 (2.6), [*4.2*]	4 (5.2), [*9.0*]
Vaccination complication	n (%)	–	2 (5.1), [*9.6*]	–	2 (2.6), [*4.5*]
Investigations	n (%) [e]	**4 (11.4)**	**6 (15.4), [*28.7*]**	**3 (7.9), [*12.6*]**	**9 (11.7), [*20.2*]**
Alanine aminotransferase increased	n (%) [e]	–	2 (5.1), [*9.6*]	1 (2.6), [*4.2*]	3 (3.9), [*6.7*]
Serum ferritin increased	n (%) [e]	–	2 (5.1), [*9.6*]	–	2 (2.6), [*4.5*]
Metabolism and nutrition disorders	n (%) [e]	**1 (2.9)**	**5 (12.8), [*23.9*]**	**4 (10.5), [*16.9*]**	**9 (11.7), [*20.2*]**
Decreased appetite	n (%)	–	2 (5.1), [*9.6*]	–	2 (2.6), [*4.5*]

RCP treatment		**Eculizumab**		**Pegcetacopla**	
OLP treatment schedule		**Crossover to pegcetaconlan**		**Continue pegcetaco**	**Total pegcetaco**
Actual OLP treatment		**Pegcetacopl an + eculizumab**	**Pegcetaco plan monothera**	**Pegcetaco plan monothera**	**Pegcetaco plan monothera**
SOC/PT	**Statisti**				
Musculoskeletal and connective tissue disorders	n (%) [e]	**4 (11.4)**	**8 (20.5), [*38.3*]**	**10 (26.3), [*42.2*]**	**18 (23.4), [*40.3*]**
Arthralgia	n (%)	1 (2.9)	3 (7.7), [*14.3*]	3 (7.9), [*12.6*]	6 (7.8),
Back pain	n (%)	–	2 (5.1), [*9.6*]	–	2 (2.6), [*4.5*]
Myalgia	n (%)	–	1 (2.6), [*4.8*]	3 (7.9), [*12.6*]	4 (5.2), [*9.0*]

Pain in extremity	n (%)	1 (2.9)	3 (7.7), [*14.3*]	2 (5.3), [*8.4*]	5 (6.5),
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	n (%) [e]	**–**	**–**	**3 (7.9), [*12.6*]**	**3 (3.9), [*6.7*]**
Nervous system disorders	n (%) [e]	**3 (8.6)**	**5 (12.8), [*23.9*]**	**8 (21.1), [*33.7*]**	**13 (16.9), [*29.1*]**
Dizziness	n (%)	–	1 (2.6), [*4.8*]	2 (5.3), [*8.4*]	3 (3.9), [*6.7*]
Headache	n (%) [e]	2 (5.7)	3 (7.7), [*14.3*]	5 (13.2), [*21.1*]	8 (10.4), [*17.9*]
Sciatica	n (%)	–	–	2 (5.3), [*8.4*]	2 (2.6), [*4.5*]
Psychiatric disorders	n (%) [e]	**–**	**2 (5.1), [*9.6*]**	**4 (10.5), [*16.9*]**	**6 (7.8), [*13.4*]**
Anxiety	n (%)	–	2 (5.1), [*9.6*]	2 (5.3), [*8.4*]	4 (5.2), [*9.0*]
Sleep disorder	n (%)	–	–	2 (5.3), [*8.4*]	2 (2.6), [*4.5*]
Renal and urinary disorders	n (%) [e]	**–**	**5 (12.8), [*23.9*]**	**6 (15.8), [*25.3*]**	**11 (14.3), [*24.6*]**
Acute kidney injury	n (%)	–	1 (2.6), [*4.8*]	3 (7.9), [*12.6*]	4 (5.2), [*9.0*]
Chromaturia	n (%)	–	2 (5.1), [*9.6*]	–	2 (2.6), [*4.5*]
Haematuria	n (%)	–	2 (5.1), [*9.6*]	1 (2.6), [*4.2*]	3 (3.9), [*6.7*]
Reproductive system and breast disorders	n (%) [e]	**1 (2.9)**	**–**	**3 (7.9), [*12.6*]**	**3 (3.9), [*6.7*]**
Respiratory, thoracic, and mediastinal	n (%) [e]	**–**	**11 (28.2), [*52.6*]**	**10 (26.3), [*42.2*]**	**21 (27.3), [*47.0*]**
Cough	n (%) [e]	–	3 (7.7), [*14.3*]	5 (13.2), [*21.1*]	8 (10.4), [*17.9*]
Epistaxis	n (%)	–	1 (2.6), [*4.8*]	2 (5.3), [*8.4*]	3 (3.9), [*6.7*]
Nasal congestion	n (%)	–	2 (5.1), [*9.6*]	–	2 (2.6), [*4.5*]
Oropharyngeal pain	n (%) [e]	–	3 (7.7), [*14.3*]	3 (7.9), [*12.6*]	6 (7.8), [*13.4*]
Rhinitis allergic	n (%)	–	2 (5.1), [*9.6*]	–	2 (2.6), [*4.5*]
Skin and subcutaneous tissue disorders	n (%) [e]	**–**	**9 (23.1), [*43.0*]**	**4 (10.5), [*16.9*]**	**13 (16.9), [*29.1*]**
Night sweats	n (%)	–	2 (5.1), [*9.6*]	–	2 (2.6), [*4.5*]
Vascular disorders	n (%) [e]	**–**	**2 (5.1), [*9.6*]**	**2 (5.3), [*8.4*]**	**4 (5.2), [*9.0*]**
Hypertension	n (%)	–	2 (5.1), [*9.6*]	1 (2.6), [*4.2*]	3 (3.9), [*6.7*]

Abbreviations: AE = adverse event; e = rate per 100 subject years; MedDRA = Medical Dictionary for Regulatory Activities; N = number of
subjects in each group; n = number of subjects in each category; OLP = Open-Label Period; PT = Preferred Term; RCP = Randomised Controlled Period; SOC = System Organ Class; TEAE = treatment-emergent adverse event.
Notes: AEs were coded to SOC and PT using MedDRA Version 23.0.
An AE (classified by PT) that occurred during the study was considered a TEAE if it had a start date on or after the first dose of investigational
product or if it had a start date before the date of the first dose but increased in severity on or after the date of the first dose. It applied up to
30 days follow-up. If a subject had multiple occurrences of a TEAE, the subject was presented only once in the subject count (n) column for a

given SOC and PT.
Only categories (defined by PT) with ⩾5% TEAEs in any group are displayed along with their corresponding SOC categories. Under a SOC
category, there may be some PT subcategories which did not meet the frequency criteria and consequently are not displayed. Thus, the sum of
AEs within the displayed PT subcategories may be fewer than the AEs indicated within the corresponding SOC category.
Source: Table 14.3.1.12.3; Table 14.3.1.12.2.

Related TEAEs

The most common individual TEAEs reported as drug-related (≥ 3 subjects in the total pegcetacoplan group) included injection site erythema (9 subjects [11.7%]), injection site induration (5 subjects [6.5%]), injection site pruritis (4 subjects [5.2%]), headache (4 subjects [5.2%]), pyrexia (3 subjects [3.9%]), and hyperbilirubinemia (3 subjects [3.9%]).

Table 50: Treatment-Emergent Adverse Events Deemed Related to Pegcetacoplan by the Investigator in ≥2% of Subjects in the Total Pegcetacoplan Group by System Organ Class and Preferred Term During the Open-Label and Follow-Up Periods (Safety Set)

RCP treatment		Eculizumab		Pegcetacopla	
OLP treatment schedule		Crossover to		Continue pegcetaco	Total pegcetaco
Actual OLP treatment		Pegcetacopl an + eculizumab	Pegcetaco plan monothera	Pegcetaco plan monothera	Pegcetaco plan monothera
SOC/PT	Statisti				
Any drug-related TEAEs	n (%)	11 (31.4)	18 (46.2)	15 (39.5)	33 (42.9)
General disorders and administration site	n (%)	7 (20.0)	11 (28.2)	8 (21.1)	19 (24.7)
Injection site erythema	n (%)	6 (17.1)	6 (15.4)	3 (7.9)	9 (11.7)
Injection site induration	n (%)	1 (2.9)	2 (5.1)	3 (7.9)	5 (6.5)
Injection site pruritus	n (%)	1 (2.9)	3 (7.7)	1 (2.6)	4 (5.2)
Injection site pain	n (%)	0	1 (2.6)	2 (5.3)	3 (3.9)
Pyrexia	n (%)	0	1 (2.6)	2 (5.3)	3 (3.9)
Gastrointestinal disorders	n (%)	3 (8.6)	5 (12.8)	2 (5.3)	7 (9.1)
Diarrhoea	n (%)	1 (2.9)	2 (5.1)	0	2 (2.6)
Blood and lymphatic system disorders	n (%)	1 (2.9)	6 (15.4)	0	6 (7.8)
Thrombocytopenia	n (%)	0	2 (5.1)	0	2 (2.6)
Infections and infestations	n (%)	0	3 (7.7)	2 (5.3)	5 (6.5)
Urinary tract infection	n (%)	0	1 (2.6)	1 (2.6)	2 (2.6)
Nervous system disorders	n (%)	1 (2.9)	2 (5.1)	3 (7.9)	5 (6.5)
Headache	n (%)	1 (2.9)	1 (2.6)	3 (7.9)	4 (5.2)
Investigations	n (%)	3 (8.6)	3 (7.7)	1 (2.6)	4 (5.2)
Alanine aminotransferase	n (%)	0	1 (2.6)	1 (2.6)	2 (2.6)
Hepatobiliary disorders	n (%)	0	0	3 (7.9)	3 (3.9)
Hyperbilirubinemia	n (%)	0	0	3 (7.9)	3 (3.9)
Musculoskeletal and connective tissue	n (%)	0	1 (2.6)	2 (5.3)	3 (3.9)
Respiratory, thoracic, and	n (%)	0	1 (2.6)	2 (5.3)	3 (3.9)

Skin and subcutaneous tissue	n (%)	0	2 (5.1)	0	2 (2.6)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each group; n = number of subjects in each category; OLP = Open-Label Period; PT = Preferred Term; RCP = Randomised Controlled Period; SOC = System Organ Class; TEAE = treatment-emergent adverse event.
Notes: AEs were coded to SOC and PT using MedDRA Version 23.0.
An AE (classified by PT) that occurred during the study was considered a TEAE if it had a start date on or after the first dose of investigational product or if it had a start date before the first dose but increased in severity on or after the date of the first dose. It applied up to 30 days follow-up. If a subject had multiple occurrences of a TEAE, the subject was presented only once in the subject count (n) column for a given SOC and PT. Definitely related and possibly related AEs were classified as related AEs. AEs with unknown relationship to study drug were counted as related AEs in the table.
Source: Table 14.3.1.4.3.

SAEs

Table 44: Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term During the Open-Label and Follow-Up Periods (Safety Set)

RCP treatment		**Eculizumab**		**Pegcetacoplan**	
OLP treatment schedule		**Crossover to pegcetacoplan**		**Continue pegcetacoplan**	**Total pegcetacoplan**
Actual OLP treatment		**Pegcetacoplan + eculizumab N = 35**	**Pegcetacoplan monotherapy N = 39**	**Pegcetacoplan monotherapy N = 38**	**Pegcetacoplan monotherapy N = 77**
SOC/PT	**Statistics**				
Any serious TEAEs	n %	**1 (2.9)**	**10 (25.6)**	**8 (21.1)**	**18 (23.3)**
Blood and lymphatic system disorders	n %	0	4 (10.3)	4 (10.5)	8 (10.4)
Haemolysis	n %	0	3 (7.7)	2 (5.3)	5 (6.5)
Cytopenia	n %	0	0	1 (2.6)	1 (1.3)
Haemolytic anaemia	n %	0	1 (2.6)	0	1 (1.3)
Thrombocytopenia	n %	0	0	1 (2.6)	1 (1.3)
Infections and infestations	n %	1 (2.9)	4 (10.3)	4 (10.5)	8 (10.4)
Gastroenteritis	n %	0	2 (5.1)	0	2 (2.6)
Biliary sepsis	n %	0	0	1 (2.6)	1 (1.3)
COVID-19	n %	0	0	1 (2.6)	1 (1.3)
Diverticulitis	n %	0	1 (2.6)	0	1 (1.3)
Post procedural sepsis	n %	0	1 (2.6)	0	1 (1.3)
Sepsis	n %	1 (2.9)	0	1 (2.6)	1 (1.3)
Upper respiratory tract infection	n %	0	0	1 (2.6)	1 (1.3)
Gastrointestinal disorders	n %	0	3 (7.7)	1 (2.6)	4 (5.2)
Abdominal pain	n %	0	0	1 (2.6)	1 (1.3)
Intestinal ischaemia	n %	0	1 (2.6)	0	1 (1.3)
Oedematous pancreatitis	n %	0	1 (2.6)	0	1 (1.3)
Small intestinal obstruction	n %	0	1 (2.6)	0	1 (1.3)
Respiratory, thoracic, and mediastinal disorders	n %	0	1 (2.6)	1 (2.6)	2 (2.6)
Epistaxis	n %	0	0	1 (2.6)	1 (1.3)
Hypersensitivity pneumonitis	n %	0	1 (2.6)	0	1 (1.3)
Hepatobiliary disorders	n %	0	1 (2.6)	0	1 (1.3)
Cholelithiasis	n %	0	1 (2.6)	0	1 (1.3)
Immune system disorders	n %	0	0	1 (2.6)	1 (1.3)

Allergy to immunoglobulin therapy	n %	0	0	1 (2.6)	1 (1.3)
Musculoskeletal and connective tissue disorders	n %	0	0	1 (2.6)	1 (1.3)
Haematoma muscle	n %	0	0	1 (2.6)	1 (1.3)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	n %	0	0	1 (2.6)	1 (1.3)

RCP treatment		**Eculizumab**		**Pegcetacoplan**	
OLP treatment schedule		**Crossover to pegcetacoplan**		**Continue pegcetacoplan**	**Total pegcetacoplan**
Actual OLP treatment		**Pegcetacoplan + eculizumab N = 35**	**Pegcetacoplan monotherapy N = 39**	**Pegcetacoplan monotherapy N = 38**	**Pegcetacoplan monotherapy N = 77**
SOC/PT	**Statistics**				
Diffuse B-cell lymphoma	n %	0	0	1 (2.6)	1 (1.3)
Renal and urinary disorders	n %	0	0	1 (2.6)	1 (1.3)
Acute kidney injury	n %	0	0	1 (2.6)	1 (1.3)
Reproductive system and breast disorders	n %	0	0	1 (2.6)	1 (1.3)
Ovarian cyst	n %	0	0	1 (2.6)	1 (1.3)
Vascular disorders	n %	0	0	1 (2.6)	1 (1.3)
Deep vein thrombosis	n %	0	0	1 (2.6)	1 (1.3)

Deaths

Table 45: Treatment-Emergent Adverse Events Leading to Death During the Open-Label and Follow-Up Periods (Safety Set)

RCP treatment		**Eculizumab**		**Pegcetacoplan**	
OLP treatment schedule		**Crossover to pegcetacoplan**		**Continue pegcetacoplan**	**Total pegcetacoplan**
Actual OLP treatment		**Pegcetacoplan + eculizumab N = 35**	**Pegcetacoplan monotherapy N = 39**	**Pegcetacoplan monotherapy N = 38**	**Pegcetacoplan monotherapy N = 77**
SOC/PT	**Statistics**				
Any TEAEs leading to death	n (%)	0	0	1 (2.6)	1 (1.3)
Infections and infestations	n (%)	0	0	1 (2.6)	1 (1.3)
COVID-19	n (%)	0	0	1 (2.6)	1 (1.3)

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each group; n = number of subjects in each category; OLP = Open-Label Period; PT = Preferred Term; RCP = Randomised Controlled Period; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

Notes: AEs were coded to SOC and PT using MedDRA Version 23.0.

An AE (classified by PT) that occurred during the study was considered a TEAE if it had a start date on or after the first dose of investigational product or if it had a start date before the first dose but increased in severity on or after the date of the first dose. It applied up to 30 days follow-up. If a subject had multiple occurrences of a TEAE, the subject was presented only once in the subject count (n) column for a given SOC and PT.

Source: Table 14.3.1.9.3.

Table 46: Treatment-Emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term During the Open-Label and Follow-Up Periods (Safety Set)

RCP treatment	**Eculizumab**	**Pegcetacoplan**	
OLP treatment schedule	**Crossover to pegcetacoplan**	**Continue pegcetacoplan**	**Total pegcetacoplan**

Actual OLP treatment		Pegcetacoplan + eculizumab N = 35	Pegcetacoplan monotherapy N = 39	Pegcetacoplan monotherapy N = 38	Pegcetacoplan monotherapy N = 77
SOC/PT	**Statistics**				
Any TEAEs	n (%)	0	6 (15.4)	2 (5.3)	8 (10.4)
Blood and lymphatic system disorders	n (%)	0	4 (10.3)	0	4 (5.2)
Haemolysis	n (%)	0	2 (5.1)	0	2 (2.6)
Bone marrow failure	n (%)	0	1 (2.6)	0	1 (1.3)
Haemolytic anaemia	n (%)	0	1 (2.6)	0	1 (1.3)
Gastrointestinal disorders	n (%)	0	1 (2.6)	0	1 (1.3)
Intestinal ischaemia	n (%)	0	1 (2.6)	0	1 (1.3)
Infections and infestations	n (%)	0	0	1 (2.6)	1 (1.3)
COVID-19	n (%)	0	0	1 (2.6)	1 (1.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	n (%)	0	0	1 (2.6)	1 (1.3)
Diffuse large B-cell lymphoma	n (%)	0	0	1 (2.6)	1 (1.3)
Respiratory, thoracic, and mediastinal disorders	n (%)	0	1 (2.6)	0	1 (1.3)
Hypersensitivity pneumonitis	n (%)	0	1 (2.6)	0	1 (1.3)

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each group; n = number of subjects in each category; OLP = Open-Label Period; PT = Preferred Term; RCP = Randomised Controlled Period; SOC = System Organ Class; TEAE = treatment-emergent adverse event.
Notes: AEs were coded to SOC and PT using MedDRA Version 23.0.
An AE (classified by PT) that occurred during the study was considered a TEAE if it had a start date on or after the first dose of investigational product or if it had a start date before the first dose but increased in severity on or after the date of the first dose. It applied up to 30 days follow-up. If a subject had multiple occurrences of a TEAE, the subject was presented only once in the subject count (n) column for a given SOC and PT.
Source: Table 14.3.1.8.3.

Immunogenicity

Of all subjects in OLP, none were confirmed positive for anti–pegcetacoplan peptide antibody at any time point (BAL-18-503-006).

Three subjects (03009002, 04001001, and 10002001) were observed to develop treatment boosted anti–polyethylene glycol antibody response in the LP as demonstrated by a ≥4-fold increase in titer from the predose level (BAL-18-503-010).

2.6.8.8. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

The safety data for pegcetacoplan in subjects with paroxysmal nocturnal hemoglobinuria (PNH) via subcutaneous (SC) infusion are mainly coming from the ongoing pivotal phase 3 study APL2-302. Supportive data coming from 3 phase 1b/2a studies (study 204, study 202 and study CP0514) are also provided. Data pooling could not be performed.

Through the data cut-off date (31 May 2020), the safety database consisted of 110 patients with PNH who received SC pegcetacoplan in the 4 studies submitted. Only 41 PNH patients were included in pegcetacoplan randomised controlled period of phase 3 pivotal study (16 weeks) among which only 10 subjects (12.5%) received pegcetacoplan for >1 year, and no patient received pegcetacoplan for more

than 2 years. Safety database is deemed limited in terms of number of PNH patients exposed and in terms of duration of exposure. Safety data from the 32-week open-label period (OLP) of Study APL2-302 with a data cutoff date of 23 September 2020 were also provided during the procedure giving an assessment of overall safety at Week 48. Long-term safety data will be also implemented by safety results from an extension study (Study APL-307) which the due date is expected for first quarter of 2026. However, while awaiting the results of this study, long-term safety has been added as missing information in the RMP.

The pivotal study APL2-302 was composed by a run-in period of 28 days, followed by a randomized control period (RCP) of 16 weeks and by 32-week open-label period (OLP). The OLP included a 4-week run-in period of cotreatment with eculizumab and pegcetacoplan for those assigned to eculizumab during the RCP. Subjects assigned to pegcetacoplan during the RCP remained on pegcetacoplan monotherapy in the OLP.

Rigorous cardiac eligibility criteria and monitoring were implemented to discharge unanticipated cardiac risk. The observations derived from dedicated non-clinical studies do not suggest a relationship between pegcetacoplan plasma concentration and effect on QTc. Cardiac safety was assessed in the pivotal Phase 3 study, Study APL2-302, using absolute ECG parameter values, change from baseline in ECG parameters, and ECG morphology assessments. To date, no evidence of a clinically relevant trend in the incidence of cardiovascular AEs, including QT interval prolongation, has been observed in clinical studies with pegcetacoplan in healthy volunteers or PNH patients. Patients with history of QT prolongation syndrome or cardiac history or those receiving drugs with the potential to prolong QT interval were excluded from Study APL2-302. However, these patients were not excluded from studies to mitigate a specific known or anticipated cardiac risk associated with the use of pegcetacoplan. These patients were excluded to minimise confounding cardiac safety outcomes and to ensure a homogeneous population for the QT analysis which formed part of the study.

During the randomized control period, the median duration of treatment for the 41 subjects that received pegcetacoplan was 3.6 months (110.0 days), and for the 39 subjects that received eculizumab the median duration of treatment was 3.3 months (99.0 days).

Sixty-seven subjects (87.0%) completed treatment in the OLP, including 32 subjects (82.1%) in the crossover to pegcetacoplan group (28 weeks of pegcetacoplan monotherapy) and 35 subjects (92.1%) in the pegcetacoplan continuation group (48 weeks of pegcetacoplan monotherapy).

During the **run-in period**, 80 patients received the combination of pegcetacoplan and eculizumab. Of the 80 patients, 69 subjects (86.3%) experienced at least 1 TEAE. There were no TEAEs leading to death, study discontinuation, or study drug discontinuation during this period.

During this period, the most common AEs were reported in the SOC general disorders and administration site conditions (49 subjects [61.3%]) with injection site reactions reported in 46 subjects (57.5%) including injection site erythema, pruritus and swelling as the most common events. However, none injection site reactions were severe, serious, or led to study drug discontinuation.

AEs that were next more often reported were gastrointestinal disorders (16 subjects [20.0%]) including diarrhoea (6 subjects [7.5%]) and nausea (5 subjects [6.3%]) and nervous system disorders (14 subjects [17.5%]) with headache being the most common events (10 subjects [12.5%]). This is not unexpected since headache is the most common adverse reaction observed with eculizumab treatment (see SmPC).

Infections and infestations were reported in 11 subjects (13.8%) with one was of moderate maximum severity (otitis externa) and one was severe (sepsis). The event of sepsis was the only one SAE reported during the run-in period, it was considered related to both pegcetacoplan and eculizumab and was

resolved without discontinuation of both drugs. The subject was later randomly assigned to pegcetacoplan and had no subsequent TEAEs of infection.

More TEAEs were considered to be related to pegcetacoplan (44/80; 55.0%) or to the infusion (32/80; 40%), than to eculizumab (4/80; 5.0%). As subjects were already on eculizumab at study entry, and pegcetacoplan was added to eculizumab treatment during the run-in period, it was not unexpected that more TEAEs during the run-in period would have been considered related to pegcetacoplan than to eculizumab.

During monotherapy treatment in the **randomized controlled period (RCP)**, a similar percentage of subjects in both treatment groups reported at least 1 TEAE, 36 patients (87.8%) in the pegcetacoplan group and 34 patients (87.2%) in the eculizumab group. Most subjects had TEAEs with a maximum severity of mild or moderate, in the pegcetacoplan group 19 subjects (46.3%) and 9 subjects (22.0%) respectively and in the eculizumab group in 14 subjects (35.9%) and 15 subjects (38.5%) respectively.

Overall in the pegcetacoplan group there were more TEAEs in the SOCs general disorders/administration site conditions, musculoskeletal/connective tissue disorders and gastrointestinal (GI) disorders than in the eculizumab group. TEAEs in the SOC infections and infestations were equally reported in both groups whereas more TEAEs in the SOCs blood/lymphatic system disorders and nervous system disorders were reported in the eculizumab group than in the pegcetacoplan group.

There were more TEAEs in the pegcetacoplan group than the eculizumab group: 270 TEAEs (100 unique events) were reported in the pegcetacoplan group whereas 135 TEAEs (73 unique events) were reported in the eculizumab group. However, when excluding injection site reactions TEAEs, the number of TEAEs becomes almost the same between both groups (142 total TEAEs [92 unique] in the pegcetacoplan group and 134 TEAEs [73 unique]).

The **most common TEAEs** observed in the pegcetacoplan group during the RCP of the pivotal study APL2-302 were injections site reactions (ISR) with 15 subjects (36.6%) including injection site erythema (7 subjects [17.1%]) and injection site reaction (5 subjects [12.2%]), diarrhoea (9 subjects [22%]) and abdominal pain (5 subjects [12.2%]). All TEAEs of diarrhoea in the pegcetacoplan group were rated mild and did not lead to treatment discontinuation.

Adverse events of special interest

The Applicant highlighted **AESIs** injection site reactions, infections, haemolytic disorders, thrombosis, and hypersensitivity.

- During the RCP of Study APL2-302, **injection site reactions** were common and occurred in much higher percentages in pegcetacoplan group compared to eculizumab group (36.6% vs 2.6%). After injection site erythema and injection site reaction, the most frequent of them were: injection site swelling, injection site induration and injection site bruising. There were no TEAEs of ISR that were serious, severe, or led to study drug discontinuation. Six subjects (17.1%) experienced ISRs during the OPL run-in period (Weeks 17-20) and 18 subjects (23.3%) experienced ISRs during pegcetacoplan monotherapy. No subjects discontinued because of an ISR and no ISRs were severe during the OLP.
- During Study APL2-302 RCP, SOC **infections and infestations** TEAEs were equally reported in the pegcetacoplan and eculizumab groups with 12 subjects (29.3%) and 10 subjects (25.6%), respectively. The wide range of observed infections were individual and no grouping was noted but the sample size is small. Two subjects in each treatment group reported viral upper respiratory tract infection (URTI) (4.9% in pegcetacoplan group and 5.1% in eculizumab group), and 1 subject in each group reported gastroenteritis and URTI. Two subjects (4.9%) reported oral herpes exclusively in the pegcetacoplan group and 2 subjects (5.1%) reported

urinary tract infection exclusively in the eculizumab group. All other types of infections/infestations were reported in 1 subject each in pegcetacoplan group or in the eculizumab group.

A total of 42 subjects (54.5%) experienced TEAEs included in the SOC of infections and infestations during the OLP. The frequency has almost doubled compared to the RCP. Events deemed related to pegcetacoplan by the investigator were limited to nasopharyngitis (1 subject [1.3%]) and urinary tract infection (2 subjects [2.6%]). The event of COVID-19 deemed unrelated to pegcetacoplan by the investigator was the only infection TEAE that led to discontinuation due to subject death.

In addition to the serious sepsis observed during the run-in period, 3 **serious infections** were observed exclusively in the pegcetacoplan group during the RCP and none required study drug discontinuation. Although these 4 serious infections occurred, none were infections due to encapsulated bacteria. A viral upper respiratory tract infection (1.3%) was reported at the beginning of the RCP when patients were still exposed to the combination of treatment. After starting the monotherapy, 2 subjects (4.9%) in the pegcetacoplan group reported serious infections: one SAE of gastroenteritis with a maximum severity of severe, and one SAE of bacterial infection with a maximum severity of mild. Both events were deemed not related to pegcetacoplan. Eight patients (10.4%) reported a serious infection during the OLP with 2 gastroenteritis (2.6%) and 3 sepsis (3.9%) of which one biliary sepsis and one post procedural sepsis. Serious diverticulitis, COVID-19 and upper respiratory tract infection were also reported by 1 subject (1.3%) each. There have been no reports of meningococcal infection or other serious infections due to encapsulated bacteria through all studies in which patients were exposed to systemic pegcetacoplan through the last data cutoff date (23 September 2020). However, taking into account prior experience of PNH patients treated with C5 inhibitors and review of published data describing the risk of infection in patients with congenital complement deficiencies, the small sample size of the clinical trial with a short exposure and follow-up, the risk of serious infections could not be excluded and should be closely monitored. In this context, serious infections have been included as an important potential risk in the RMP. The Applicant proposes to use non-interventional registry study to evaluate the effectiveness of RMMs on reduction and mitigation of the risk of serious infections with encapsulated bacteria. From the registry data, the applicant will also monitor the extent to which the aRMMs and SmPC are followed by prescribers and the extent to which they reduce and mitigate important potential risks (particularly the risk of serious infections) to enable evaluation of the effectiveness of these measures. In addition, actualisation of appropriate vaccination or antibiotic prophylaxis in patients treated with pegcetacoplan will be captured through the system of controlled distribution. Annual reminders to prescribers or pharmacists will be used. These actions are considered appropriate to evaluate the effectiveness of risk minimisation measures. During the Study APL2-302 there were significant events of pegcetacoplan related **haemolysis** observed (9.8% vs 23.1% in pegcetacoplan and eculizumab groups, respectively). Three events led to discontinuation of pegcetacoplan during the pegcetacoplan monotherapy; two events were considered related to pegcetacoplan with no other evident cause of haemolysis and one which was not considered related to pegcetaplan was possibly explained due to obesity and suboptimal exposure. The 3 patients were withdrawn from the study and recovered from the event of haemolysis after a dose of eculizumab. In patients randomised to eculizumab group, 3 patients experienced 4 events of haemolysis that were considered definitely or possibly related to pegcetacoplan after discontinuation of pegcetacoplan after run-in period on study Day 1. No events of haemolysis occurred because of missed or delayed pegcetacoplan or eculizumab doses. A total of 18 subjects (23.4%) experienced TEAEs in the SMQ of haemolytic disorders during the OLP. All events in the SMQ were reported by 1

subject (1.3%) with the exception of haemolysis (15 subjects, 19.5%) and haemolytic anaemia (2 patients, 2.6%). This is consistent with what was reported in the RCP.

- Only one **thrombosis** event was observed in the primary safety analysis set and 2 subjects (2.6%) had events in the MedDRA HGLT of embolism and thrombosis during the OLP.
- One case of local **hypersensitivity** TEAE was observed in Study 204, Cohort 2. No SAE of hypersensitivity was observed in the primary safety analysis set. A total of 13 subjects (16.9%) experienced TEAEs in the SMQ of hypersensitivity during the OLP. Each event was reported in 1 subject (1.3%) with the exception of acute respiratory failure and erythema which was reported in 2 subjects (2.6%).

A similar proportion of subjects in the pegcetacoplan and eculizumab groups experienced **SAEs** during the RCP: 7 subjects (17.1%) in the pegcetacoplan group experienced 8 SAEs, and 6 subjects (15.4 %) in the eculizumab group experienced 11 SAEs. The most common SAEs were in the SOC Blood and Lymphatic Disorders with twice as much SAEs in the eculizumab group than in the pegcetacoplan group. In the eculizumab group 2 subjects (5.1%) reported anaemia and 1 subject each (1.3% each) reported haemolytic anaemia and haemolysis whereas 2 subjects (4.9%) in the pegcetacoplan reported haemolysis. One subject in each treatment group had an SAE that was considered related to treatment. An atrial fibrillation was reported as an SAE in the pegcetacoplan group in 1 patient (2.4%).

During the RCP, one SAE (2.4%) of facial paralysis in the pegcetacoplan group was considered related to study drug (pegcetacoplan), and one SAE (2.6%) of pyrexia in the eculizumab group was considered related to study drug (eculizumab).

More SAEs (18 patients, 23.3%) were observed during the OLP than in the RCP. The most common SAEs were in the SOC blood and lymphatic disorders and in the SOC infections and infestations (8 patients, 10.4% each). Each SAE was reported by 1 subject (1.3%) with the exception of haemolysis and gastroenteritis. Haemolysis was reported for 5 subjects (6.5%) and gastroenteritis was reported for 2 subjects (5.1%); neither event resulted in discontinuation. Three serious event of sepsis (biliary sepsis, sepsis and one post procedural sepsis) were reported during the OLP.

A warning has been added to the SmPC section 4.4 that patients with PNH should be monitored regularly for signs and symptoms of haemolysis, including measuring LDH levels, and may require dose adjustment within the recommended dosing schedule.

There may be interference between silica reagents in coagulation panels and pegcetacoplan that results in artificially prolonged activated partial thromboplastin time (aPTT); therefore, a warning has been added to section 4.4 of the SmPC that the use of silica reagents in coagulation panels should be avoided.

No **deaths** occurred in the pivotal study APL2-302 before Week 16. One death was reported during the OLP due to a fatal SAE of severe COVID-19 deemed not related to pegcetacoplan by the investigator.

Other findings

Overall, the **laboratory findings** were consistent with those expected in PNH patients. Observed changes in laboratory findings were reflective of pegcetacoplan efficacy findings. It is agreed with the Applicant that there is no safety signal regarding laboratory findings from the primary safety analysis set.

Few cases of **QT prolongation** were observed in the primary safety analysis.

Discontinuations due to the AEs

Overall, the number of **discontinued** subjects was not negligible (10% in Study APL2-302, 0 to 14.3% in ongoing PNH and other ongoing systemic-use studies). There were in total 5 cases of pegcetacoplan

discontinuations due to TEAEs in the primary safety analysis set. During the RCP, 3 subjects (7.3%) discontinued because of TEAEs, all in the pegcetacoplan group, and all because of breakthrough haemolysis, 1 was a SAE and 2 TEAEs were designated as pegcetacoplan related, both resolved with intervention. More details about these 3 cases are needed. There were in total 11 cases of discontinuations due to AEs in Study APL2-302 thorough 31 May 2020 cut-off date. Six of those were designated as pegcetacoplan related. Three were observed during open-label phase: intestinal ischaemia, hypersensitivity pneumonitis and haemolytic anaemia, and they were SAEs.

There were 10 (13%) discontinuations from study treatment including 9 discontinuations due to an AE during the OLP with no trend in the nature of AEs leading to discontinuation.

Supportive studies

The number of patients enrolled in the 3 supportive studies (respectively 4 patients in study 202, 20 patients in cohort 2 of study 204 and 6 patients in cohort 4 of study CP0514) is low compared with the number of patients enrolled in the pivotal study APL2-302 (80 patients). The posology between the 3 supportive studies and the pivotal study is also different. The interpretation of percentage of TEAEs observed in the 3 supportive studies and the comparison with what was observed in the pivotal study are thus hampered. However, safety results in these 3 supportive studies are as follows:

Among the 4 subjects in Study 202, the most common TEAEs were dizziness and erythema that occurred in 2 subjects each (50%).

Among the 20 patients in cohort 2 of the Study 204, the most common TEAEs were upper respiratory tract infection (5 subjects [25.0%]), injection site erythema (4 subjects [20.0%]) and hypokalemia (4 subjects [20.0%]).

Among the 6 patients of the cohort 4 in Study CP0514, the most common TEAEs were headache (5 subjects [83.3%]), injection site bruising (4 subjects [66.7%]) and injection site pain (4 subjects [66.7%]).

Drug-related TEAEs reported in the 3 supportive studies Study 202, Study 204, and Study CP0514 are consistent with what was observed in the pivotal study with the drug related injection site reactions that were commonly reported. ISRs occurred in 2 subjects (50.0%) in Study 202, 8 subjects (40.0%) in Study 204, and 5 of 6 subjects in Study CP0514. Study APL2-302, no ISRs were severe or led to discontinuation in these studies.

Two SAEs of ALT and AST increased were observed in one patient each (12.5%) and were deemed related to pegcetacoplan in the study CP-0514.

No deaths occurred in the study 202 but 3 deaths occurred in the Study 204 and CP0514, 2 of which were on-study (aplastic anaemia in the cohort 2 of the study 204 and intracranial haemorrhage in the cohort 1 of the study CP0514) whereas the last was not on study (abdominal neoplasm in the cohort 2 of the study 204) and none of which were deemed related to pegcetacoplan by the investigator.

Among the 3 supportive studies, 3 subjects in Cohort 2 of the study 204 experienced SAEs that led to pegcetacoplan discontinuation: a fatal SAE of aplastic anaemia and a severe SAE of abdominal neoplasm that were both deemed not related to pegcetacoplan by the investigator and that led to pegcetacoplan discontinuation and subjects' discontinuation from the study. A moderate SAE of hypersensitivity that was deemed related to pegcetacoplan by the investigator led also to pegcetacoplan discontinuation.

Four serious infections were observed in the study CP0514, one sepsis and 3 urinary tract infections.

Immunological events

There are uncertainties regarding immunogenicity testing method and multiple PK OCs are raised. Antigenicity was observed during repeat-dose toxicity studies (non-clinical development). Pegcetacoplan was weakly to moderately immunogenic in rabbits and minimally immunogenic in monkeys. But, the assay used is not completely reliable. In addition, in Compliance statements of several studies (13-catx-004, 14catx-001, 14-catx-002, 14-catx-005, and 15catx-004), an exception from GLP is reported: scientific interpretation of the antigenicity results were not performed in accordance with GLP regulations. In the clinical development program, there were high percentages of pre-existing anti-PEG antibodies (up to 82.5%). In Study APL2-302 RCP, two subjects (2.5%) had a positive anti-pegcetacoplan peptide antibody response. Furthermore, one subject developed treatment-emergent anti-PEG antibody response, and one subject developed treatment-boosted anti-PEG antibody response. Both events are considered transient. In Study 204, Cohort 2 one subject had TEAE of rash maculo-papular deemed related to pegcetacoplan by the investigator. This event was temporally associated with positive serum anti-PEG antibodies.

Overall immunogenicity are consistent across all clinical studies with infrequent and generally transient anti–pegcetacoplan peptide antibody responses detected in pegcetacoplan-treated subjects, a high percentage of preexisting anti-PEG antibody responses reported in the predose samples and a low incidences of treatment-emergent or treatment-boosted anti-PEG antibody response, with many of those responses that were transient.

Presented data are thus reassuring. However, results related to immunogenicity in the pivotal Study APL2-302 are immature and the Applicant has been requested to provide further data on immunogenicity. As such, Immunogenicity has been added as an important potential risk in the EU RMP and has been included as a safety concern to be monitored in the PASS (please refer to the RMP).

Interactions

According to the available data, the potential of pegcetacoplan for drug-drug interactions is low. There is an experience of concomitant use of pegcetacoplan and eculizumab obtained during Study APL2-302 and Study CP0514. It is agreed with the Applicant that there was no apparent safety issue during concomitant use of pegcetacoplan and eculizumab in Study APL2-302.

There may be interference between silica reagents in coagulation panels and PEGylated pegcetacoplan that results in artificially prolonged activated partial thromboplastin time.

Non-clinical findings

Nonclinical findings with potential to affect clinical use included epithelial vacuolation and infiltration of vacuolated macrophages to multiple tissues including renal findings (renal tubular vacuolation) which were seen in repeat-dose primate studies. For the time being, these do not appear to correlate with adverse renal effects in human use, according to limiting available data. However, the risk of PEG accumulation and especially the risk of renal effects needs to be monitored and have been added as an important potential risk in the RMP. Reproductive and developmental toxicity studies have been conducted in rabbits and rats with no effects on maternal or foetal endpoints after pegcetacoplan SC administration. The reproductive toxicity study in *Cynomolgus* monkeys found several spontaneous abortions and *in utero* deaths. The human relevance of these findings is unclear because contraception was required in all clinical studies.

Special population

One study in subjects with renal impairment, Study 205, has been performed. Pegcetacoplan was well tolerated across both the severe renal impairment and control cohorts with no major differences between cohorts other than ongoing TEAEs and concomitant medications reflective of the underlying medical

condition and not pegcetacoplan treatment. No dose adjustment is warranted in patients with hepatic impairment.

The pivotal Study APL2-302 did not include children or adolescents. A PIP waiver was given for the paediatric population aged <12 years whilst a PIP is in place for the paediatric subset aged from 12 years to less than 18 years and a phase study 2 is ongoing in paediatric patients.

There are no data on use of pegcetacoplan during pregnancy and breastfeeding, except for one case of pregnancy that was reported in Study CP0514, Cohort 4 with no adverse effect on pregnancy, mother or child.

Safety data in *elderly* are awaited.

Other considerations

Of note, C5-inhibitors have an important potential risk of malignancies and haematological abnormalities. It is agreed with the Applicant that a potential risk of malignancies and haematological abnormalities cannot be excluded. This has been reflected in the RMP and "malignancies and haematological abnormalities" is an important potential risk.

There are uncertainties regarding long-term PEG accumulation effects also considered as an important potential risk in the RMP.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

Additional expert consultation

NA.

Assessment of paediatric data on clinical safety

The pivotal Study APL2-302 did not include children or adolescents. A PIP waiver was given for the paediatric population aged <12 years whilst a PIP is in place for the paediatric subset aged from 12 years to less than 18 years. A paediatric nonrandomised study of subjects aged 12 to 17 years (Study 209) is ongoing. This study is an open-label, single-arm, Phase 2 Study whose objectives are to assess safety and tolerability, PK, and biological activity (including efficacy and pharmacodynamics [PD]) of multiple subcutaneous doses of pegcetacoplan in paediatric patients with PNH. Twelve subjects planned. The final report is expected for 2024.

2.6.10. Conclusions on the clinical safety

With respect to the available information coming from a limited safety database with a limited follow-up, pegcetacoplan adds a mild additional toxicity to the target population treated with the proposed dose regimen of 1080 mg twice weekly subcutaneous infusion. However, the limited safety database does not allow to comprehensively determine the safety profile of pegcetacoplan in the absence of comparative long-term safety data especially in setting of concerned indication with chronic use.

The safety of pegcetacoplan appears to be comparable to eculizumab in this randomized controlled Phase 3 study, with a similar incidence of AEs and SAEs between both groups.

The most common AEs observed during the randomized controlled treatment period were injection site reactions (ISRs) (36.6%), all types of infection (29.3%), diarrhoea (22%), abdominal pain (12.2%) and

haemolysis (9.8%) with pegcetacoplan and haemolysis (23.1%), headache (23.1%), fatigue (15.4%), back pain (10.3%) and abdominal pain (10.3%) with eculizumab. While some TEAEs occurred more frequently in the pegcetacoplan group (eg, ISRs and diarrhoea), others occurred more frequently in the eculizumab group (eg, haemolysis and headache). Infections were equally reported in the both groups. TEAEs such as ISRs and diarrhoea that occurred more frequently in the pegcetacoplan group did not limit overall tolerability, as none were serious, severe, or led to study drug discontinuation. The most common AEs reported in the open-label phase (OLP) were ISRs (23.4%), haemolytic disorders (23.4%), nasopharyngitis (15.6%), and diarrhoea (13.0%). The incidence of ISRs and diarrhoea was lower in the OLP than in the RCP.During the randomized control period, the most common SAE observed in the pegcetacoplan group was haemolysis (4.9%) and in the eculizumab group was anaemia (5.1%). Overall from the run-in period and over Week 16 (with preliminary results from the open-label phase), the most common SAEs reported with pegcetacoplan treatment were haemolysis (10.0%), abdominal pain (3.8%), gastroenteritis (3.8%), and sepsis (3.8%).

Serious infections were reported with pegcetacoplan exposure but none were infections due to encapsulated bacteria. Serious infections have been added as important potential risk in the RMP with additional risk mitigation measure using registry data.

More serious events of haemolysis or that led to study drug discontinuation were observed in the pegcetacoplan group although AEs of haemolysis occurred more frequently in the eculizumab group. There are uncertainties regarding immunogenicity testing method from the PK point of view that preclude conclusions on immunogenicity of pegcetacoplan. Immunogenicity has been added as an important potential risk in the RMP and has been included as a safety concern to be monitored in the PASS (Study APL2-302 and Study 307).

Safety data from the OLP were consistent with what was previously observed with pegcetacoplan treatment. Most subjects had TEAEs with a maximum severity of mild or moderate during the OLP. The majority of AEs were not serious and there were no unexpected events and no AEs of meningitis. However, full safety results for Study APL2-302, compiling data across all periods of the study, are not yet available. Long-term safety has been added as missing information in the RMP.

The applicant committed to conduct the following Post-Authorization Safety Studies (PASS), Category 3, as reflected in the RMP:

- PASS using registry data for pegcetacoplan, to evaluate the occurrence of serious infections in patients with PNH treated with pegcetacoplan.

- PASS using registry data for pegcetacoplan, to evaluate data on pregnancy outcomes

In addition, the Applicant will continue study Study APL2-302 (To establish the efficacy and safety of pegcetacoplan compared with eculizumab in subjects with PNH who continue to have Hb levels <10.5 g/dL despite treatment with eculizumab) and study 307 (to evaluate the long-term safety and efficacy of pegcetacoplan in subjects with PNH)

The Applicant commits to submit a Type II variation to update the SmPC in order to reflect the final Study APL2-302 48-week data.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table: Summary of safety concerns

Important identified risks	None
Important potential risks	1. Serious infections 2. Serious hypersensitivity reactions 3. Intravascular haemolysis after drug discontinuation 4. Immunogenicity 5. Malignancies and haematologic abnormalities 6. Potential long-term effects of PEG accumulation
Missing information	1. Use in patients with bone marrow failure 2. Use in pregnant women 3. Long-term safety (>1 year)

2.7.2. Pharmacovigilance plan

Table: Ongoing and Planned Additional Pharmacovigilance Activities

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1—Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Category 2—Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Category 3—Required additional pharmacovigilance activities *(by the competent authority)*				
PASS using registry data for pegcetacoplan Planned	To evaluate the occurrence of serious infections in patients with PNH treated with pegcetacoplan	• Serious infections • Serious hypersensitivity reactions • Intravascular haemolysis after drug discontinuation • Immunogenicity • Malignancies and haematological abnormalities • Potential long-term of effects of PEG accumulation • Use in patients with bone marrow failure • Long-term safety	Submission of final protocol Start of data collection: End of data collection: Interim study reports: Progress report: Final study report:	Within 6 months of marketing authorisation Q3/Q4 2022 Q4 2027 Annually throughout the PASS Twice per year until the end of the study <1 year after last patient, last visit

PASS using registry data for pegcetacoplan Planned	To evaluate data on pregnancy outcomes	• Missing information: Use in pregnant women	Submission of final protocol Start of data collection: End of data collection: Interim study reports: Final study report:	Within 6 months of marketing authorisation Q3/Q4 2022 Q4 2032 Annually throughout the PASS <1 year after the outcome of the last pregnancy observed is obtained

Study APL2-302 Ongoing	To establish the efficacy and safety of pegcetacoplan compared with eculizumab in subjects with PNH who continue to have Hb levels <10.5 g/dL despite treatment with eculizumab	• Serious infections • Serious hypersensitivity reactions • Intravascular haemolysis after drug discontinuation • Immunogenicity • Malignancies and haematological abnormalities • Potential long-term of effects of PEG accumulation	Final report	January 2022
Study 307 Ongoing	To evaluate the long-term safety and efficacy of pegcetacoplan in subjects with PNH	• Serious infections • Serious hypersensitivity reactions • Intravascular haemolysis after drug discontinuation • Immunogenicity • Malignancies and haematological abnormalities • Potential long-term effects of PEG accumulation • Long-term safety	Final report	Q1 2026

Abbreviations: Hb = haemoglobin; PASS = postauthorisation safety study; PEG = polyethylene glycol; PNH = paroxysmal nocturnal haemoglobinuria; Q = Quarter.

2.7.3. Risk minimisation measures

Table: Summary of risk minimisation measures

Safety concern	Risk minimisation measures
Serious infections	Routine risk minimisation measures: • Summary of Product Characteristics (SmPC) Section 4.3, Section 4.4, and Section 4.8 • Package Leaflet Section 2, Section 3, and Section 4 Additional risk minimisation measures: • Guide for healthcare professionals • Patient card • Patient/carer guide • Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines) • System for controlled distribution
Serious hypersensitivity reactions	Routine risk minimisation measures: • SmPC Section 4.3 and Section 4.4 • Package Leaflet Section 2 Additional risk minimisation measures: • Guide for healthcare professionals • Patient/carer guide
Intravascular haemolysis after drug discontinuation (PNH)	Routine risk minimisation measures: • SmPC Section 4.2 and Section 4.4 • Package Leaflet Section 2, Section 3, and Section 4 Additional risk minimisation measures: • Guide for healthcare professionals • Patient/carer guide
Immunogenicity	Routine risk minimisation measures: • SmPC Section 4.8 Additional risk minimisation measures:

	• None
Malignancies and haematologic abnormalities	Routine risk minimisation measures: • None Additional risk minimisation measures: • None
Potential long-term effects of PEG accumulation	Routine risk minimisation measures: • SmPC Section 4.4 and Section 5.3 Additional risk minimisation measures: • Guide for healthcare professionals
Use in patients with bone marrow failure	Routine risk minimisation measures: • None Additional risk minimisation measures: • None
Use in pregnant women	Routine risk minimisation measures: • SmPC Section 4.4, Section 4.6 and Section 5.3 • Package Leaflet Section 2 Additional risk minimisation measures: • None
Long-term safety (>1 year)	Routine risk minimisation measures: • SmPC Section 4.2, Section 4.4, Section 4.6, Section 4.8, and Section 5.2 • Package Leaflet Section 4 Additional risk minimisation measures: • None

2.7.4. Conclusion

The CHMP considered that the risk management plan version 0.4 is acceptable.

In addition, the following minor revisions are recommended to be taken into account with the next RMP update: The applicant should replace the content of annex 6 by that of PI annex IID, subsection "Additional risk minimisation measures".

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 14.05.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The request to use minimum particulars for the 20 mL vial label was accepted by the QRD group, based on the fact that therapy will be initiated under the supervision of a healthcare professional experienced in the management of patients with haematological disorders, and that before self-administration is initiated, patient will be instructed by a qualified healthcare professional in infusion techniques, the use of a syringe system infusion pump, the keeping of a treatment record, the recognition of possible adverse reactions, and measures to be taken in case these occur. All the relevant particulars are listed on the outer carton, moreover, the medicine should be protected from light and as such should not be removed from its outer carton until it is being prepared.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Aspaveli (pegcetacoplan) is included in the

additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months.

3.1.2. Available therapies and unmet medical need

To most effectively manage PNH, both IVH and EVH need to be controlled. This is reflected in improvements across the following key markers of disease activity: hemoglobin level, LDH level, ARC, bilirubin level, transfusion requirements, and FACIT-Fatigue score. The C5 inhibitors (eculizumab and ravulizumab), the only currently available treatments, have increased survival and improved outcomes in PNH by controlling IVH, reflected in LDH improvements; however, C5 inhibitors do not control EVH. In many patients treated with C5 inhibitors, although LDH is largely controlled, ARC and bilirubin levels remain elevated, indicative of ongoing hemolysis. Despite the availability of eculizumab over the past 13 years, patients remain symptomatically limited by their disease and still require PRBC transfusion because not all key markers of disease activity are meaningfully improved. Considering the available therapies, there is no unmet medical need. However, new therapies that provide more complete control are needed.

3.1.3. Main clinical studies

Study APL2-302 is the pivotal study submitted to provide the evidence of efficacy and safety. This study is a global, Phase 3, prospective, randomized, multicenter, open-label, active comparator controlled study. Its objective is to confirm treatment efficacy and safety of pegcetacoplan monotherapy for the treatment of PNH in subjects aged ≥18 years who were receiving eculizumab therapy but continued to have Hb levels <10.5 g/dL. This target population is reflected in the SmPC. Subjects were randomized to receive pegcetacoplan 1080 mg twice weekly or every 3 days if clinically indicated or their current dosage of eculizumab. This head-to-head comparator trial was designed to demonstrate superiority of pegcetacoplan to eculizumab monotherapy in subjects with PNH currently on treatment with eculizumab as measured by change in Hb level at Week 16. The 16-week RCP is completed; the 32-week open-label period is ongoing.

The study enrolled 80 subjects; 41 in pegcetacoplan arm and 39 in eculizumab arm.

The applicant further submitted efficacy and safety data from the Study APL2-302 open-label period from Week 17 through Week 48 + follow-up with a data cut-off date of 23 September 2020. 77

patients were enrolled, completed the Week 48 visit and had either entered follow-up or the extension study, Study APL2-307.

3.2. Favourable effects

With the MMRM analysis, the least-square (LS) mean CFB in Hb at Week 16 in the pegcetacoplan and eculizumab groups was 2.37 g/dL and -1.47 g/dL, respectively. The difference in LS mean CFB in Hb between the 2 groups of 3.84 g/dL was statistically significant (95% CI 2.33, 5.34; P<.0001) and higher than the pre-specified difference between pegcetacoplan and eculizumab of 1 g/dl. The primary endpoint has been reached. A large number of subjects received transfusions in eculizumab arm (n=33) compared to pegcetacoplan arm (n=5). These data reflect a superiority of pegcetacoplan compared to eculizumab in terms of efficacy of control of the disease. The Applicant has provided additional sensitivity analyses of primary efficacy endpoint (based on imputation methods) and supportive analyses of primary efficacy endpoint data with all available data (uncensored for transfusion) which confirm this primary analysis.

With regards to key secondary endpoints, pegcetacoplan met non-inferiority to eculizumab on transfusion avoidance, with 85.4% of pegcetacoplan subjects and 15.4% of eculizumab subjects achieving transfusion avoidance (nominal P value <.0001). This result is significantly clinically relevant. The proportion of subjects who were transfusion avoidant was similar in the pegcetacoplan group, regardless of baseline PRBC transfusion strata or baseline platelet strata, but not in the eculizumab group. Pegcetacoplan was also non-inferior to eculizumab for CFB in ARC, a marker of hematopoietic bone marrow compensatory activity in the setting of anemia and/or hemolysis, with an LS mean difference of −163.6 × 109 cells/L (nominal P value <.0001). LDH did not meet non-inferiority by the prespecified analysis. However, a greater percentage of subjects on pegcetacoplan achieved LDH normalization, as compared with eculizumab (71% vs 15%, respectively). Non-inferiority for the FACIT-Fatigue score was not assessed because of the prespecified hierarchical testing. Of note, higher numerical improvements were seen in FACIT-Fatigue score in the pegcetacoplan group as compared with the eculizumab group with a difference of 11.87 points (95% CI 5.49, 18.25; nominal P value 0.0005).

Improved outcomes with pegcetacoplan treatment, as compared with eculizumab treatment, were observed in others secondary endpoints at Week 16. Higher percentage of subjects in the pegcetacoplan group, as compared with the eculizumab group, achieving Hb response (75.6 % vs 0%), Hb normalization (34.1% vs 0%), and ARC normalization (78% vs 2.6%). Subjects in the pegcetacoplan group required fewer units of PRBCs to be transfused. The mean number of PRBC units required in the pegcetacoplan group was 0.6 and in the eculizumab group was 5.1 (95% CI: 2.0, 4.0). Indirect bilirubin levels decreased with pegcetacoplan treatment, but not with eculizumab treatment. LASA and QLQ-C30 scores increased in pegcetacoplan arm but not in eculizumab arm. However, no clear differences were seen between treatment groups in haptoglobin levels.

Analyses based on stratification factors were in line with the primary analyses.

Signs of breakthrough haemolysis while LDH elevated (after prior reduction of LDH) was observed in 2 subjects (4.9%) in pegcetacoplan and 13 subjects (33.3%) in eculizumab arm.

When all observed data were considered (no censoring of data due to PRBC transfusion), the results of all primary and key secondary analyses were consistent with the MMRM analyses in which post-transfusion data were set to missing.

Regarding Transfusion Avoidance at Week 48, fifty-five subjects (71.4%) in the total pegcetacoplan monotherapy group did not require transfusions, including 24 subjects (61.5%) in the crossover to pegcetacoplan group and 31 subjects (81.6%) in the pegcetacoplan continuation group. Moreover,

subjects randomised to the eculizumab group during the crossover to pegcetacoplan group who failed to demonstrate improvement during the RCP showed improvement after restarting pegcetacoplan in the OLP.

Results of the key efficacy analyses of the OLP confirm the results observed during the 16-week RCP, suggest an improvement in PNH markers and fatigue and efficacy results were comparable to that observed for the pegcetacoplan continuation group. The PK analysis within OLP showed that therapeutic concentrations of pegcetacoplan were maintained for up to Week 48.

3.3. Uncertainties and limitations about favourable effects

Because subjects in this study had to maintain their regular intravenous eculizumab dosing schedule during the run-in period, as well as receive twice-weekly subcutaneous pegcetacoplan, a double-blind study design was not possible, and a double-dummy design was not considered feasible by the Applicant. This is understood but is a limitation. Specific measures of minimisation of bias are outlined and it is acknowledged that the need of transfusions and the classification of patients as responders/non responders was done following objective lab tests criteria regardless of investigator opinion.

Some imbalances in clinical baseline characteristics are observed, with more participants in eculizumab group compared to pegcetacoplan having the following: ≥4 transfusions in the last 12 months; higher mean LDH levels and more profoundly reduced haptoglobin, however, it seems that there was a number of censored observations in the eculizumab group.

A GCP non-compliant site from the US that enrolled 2 patients was closed, but the patients were included in the ITT analysis. Their inclusion in the ITT set is questionable, but it can be considered justified. Sensitivity analysis provides confirmation of consistency with a main analysis.

Eculizumab is underperforming in the pivotal study compared to published studies. However, under-performance of eculizumab cannot easily be concluded because patient populations in the pegcetacoplan, eculizumab and ravulizumab pivotal trials were different.

3.4. Unfavourable effects

The safety profile of pegcetacoplan in the treatment of PNH patients, priory C5i-treated, is based mainly on one phase 3 and 3 supportive clinical trials: Phase 3 Study APL2-302 in C5i-treated subjects with proposed dosage of pegcetacoplan 1080 mg SC twice weekly (pegcetacoplan, N=41; eculizumab, N=39); 3 supportive Phase 1b/2a studies, Study 202 [C5i-naive subjects] (N=4), Study 204 [C5i-naive subjects] (Cohort 2, N=20), and Study CP0514 [C5i-treated subjects] (Cohort 4, N=6) with dosing 270 mg/day SC or higher, but sufficiently comparable with proposed dosing. Data pooling could not be performed.

With respect to the available information, pegcetacoplan adds a mild additional toxicity to the target population treated with the proposed dose regimen of 1080 mg twice weekly subcutaneous infusion. This is clinically characterised by TEAEs as injection site reactions (ISRs) (36.6%), all type of infections (29.3%), diarrhoea (22%), injection site erythema (17.1%), injection site reaction (12.2%), abdominal pain (12.2%), haemolysis (9.8%), injection site swelling (9.8%), asthenia (7.3%), injection site induration (7.3%), back pain (7.3%), pain in extremity (7.3%), headache (7.3%) and hypertension (7.3%) observed in ≥ 5% of the patients in the paroxysmal nocturnal hemoglobinuria (PNH) population.

Before Week 16 (from the run-in period to the end of the randomized control period) of the Study APL2-302, the most common SAEs (≥1%) were haemolysis (4.9%), bacterial infection (2.4%),

gastroenteritis (2.4%), atrial fibrillation (2.4%), pyrexia (2.4%), facial paralysis (2.4%), dyspnoea (2.4%) and sepsis (1.3%). In the open-label period (OLP), the most common SAEs were in the SOC blood and lymphatic disorders and in the SOC infections and infestations (8 patients, 10.4% each). Each SAE was reported by 1 subject (1.3%) with the exception of haemolysis and gastroenteritis. Haemolysis was reported for 5 subjects (6.5%) and gastroenteritis was reported for 2 subjects (5.1%)

Overall, from the run-in period and over Week 16 (with preliminary results from the open-label phase) of the Study APL2-302, the most common SAEs (≥2%) reported with pegcetacoplan treatment were haemolysis (10.0%), abdominal pain (3.8%), gastroenteritis (3.8%), sepsis (3.8%), infection (2.5%), haemolytic anaemia (2.5%) and anaemia (2.5%). Six subjects had SAEs which were designated as pegcetacoplan related by the investigator: haemolytic anaemia, intestinal ischaemia (reported with intrahepatic Budd-Chiari syndrome), biliary sepsis, sepsis, facial paralysis, and hypersensitivity pneumonitis. None led to treatment withdrawal.

One death was reported during the OLP of the study APL2-302 due to a fatal SAE of severe COVID-19 deemed not related to pegcetacoplan by the investigator. One on-study death occurred in Study 204, Cohort 2. It was due to serious TEAE aplastic anaemia (AA) which is designated as not related to pegcetacoplan by investigator.

While some TEAEs occurred more frequently in the pegcetacoplan group (e.g., injection site reactions and diarrhoea), others occurred more frequently in the eculizumab group (e.g., haemolysis and headache). Infections were equally reported in the both groups.

Adverse events of special interest (AESIs) include injection site reactions, infections, haemolytic disorders, thrombosis, and hypersensitivity.

Injections site reactions (ISR) were the most commonly reported TEAEs in the pegcetacoplan group (36.6%) including injection site erythema, injection site reaction, injection site swelling, injection site induration and injection site bruising for the most of them. There were no TEAEs of ISR that were serious, severe, or led to study drug discontinuation. Most of the injection site reactions were a maximum severity of mild, with one report of moderate maximum severity. Injections site reactions were exclusively observed in pegcetacoplan group. The two events of injection site reactions in the eculizumab group were due to vaccination. During the OLP, 23.3% of subjects experienced ISRs during pegcetacoplan monotherapy. No subjects discontinued because of an ISR and no ISRs were severe during this period.

Infections and infestations were equally reported in the pegcetacoplan and eculizumab groups during the randomized control period (RCP) of the pivotal study (29.3% vs 25.6%, respectively). Overall, infections observed in both groups were for most of them upper respiratory tract infection (URTI), viral URTI and gastroenteritis. Oral herpes were exclusively observed in the pegcetacoplan group although urinary tract infection were exclusively observed in the eculizumab group. All other types of infections/infestations were reported in 1 subject each in pegcetacoplan group or in the eculizumab group. Four serious infections were observed from the run-in period to the end of the RCP, a sepsis, a viral URTI, a bacterial infection and a gastroenteritis and none required study drug discontinuation. Eight patients (10.4%) reported a serious infection during the OLP with 2 gastroenteritis (2.6%) and 3 sepsis (3.9%) of which one biliary sepsis and one post procedural sepsis. Serious diverticulitis, COVID-19 and upper respiratory tract infection were also reported by 1 subject (1.3%) each. Through all studies in which patients were exposed to systemic pegcetacoplan through the last data cutoff date (23 September 2020), none infection was meningococcal infection or other serious infections due to encapsulated bacteria.

More serious events of haemolysis (4.9% vs 2.6%) or that led to study drug discontinuation (7.3% vs 0) were observed in the pegcetacoplan group during the RCP although AEs of haemolysis occurred more frequently in the eculizumab group (9.8% with pegcetacoplan vs 23.1% with eculizumab). Two

patients reported haemolysis that were deemed related to pegcetacoplan and 2 patients (4.9%) reported a serious haemolysis (4.9%) in the pegcetacoplan group during the RCP. In the OLP, 23.4% of subjects experienced TEAEs in the SMQ of haemolytic disorders. All events in the SMQ were reported by 1 subject (1.3%) with the exception of haemolysis (15 subjects, 19.5%) and haemolytic anaemia (2 patients, 2.6%). Intravascular haemolysis after drug discontinuation is identified as important potential risk in the RMP.

In addition to these AEs, TEAEs of diarrhoea were very commonly reported (22%) in the pegcetacoplan group (compared with one subject in the eculizumab group). All TEAEs of diarrhoea in the pegcetacoplan group were rated mild and did not lead to treatment discontinuation. The TEAEs from the SOC Musculoskeletal and connective tissue disorders were also frequently reported with a greater proportion in the pegcetacoplan group (16 subjects [39%]) including for most of them back pain, pain in extremity, arthralgia and neck pain.

3.5. Uncertainties and limitations about unfavourable effects

The safety database is considered limited in terms of number of patients and in terms of follow-up. Six important potential risks are thus considered in the risk management plan (RMP): serious infections, serious hypersensitivity reactions, intravascular haemolysis after drug discontinuation, immunogenicity, malignancies and haematologic abnormalities and potential long-term effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs. Taking into account that all these risks were not observed during the pivotal study due to limited number of patients and limited follow-up, it cannot be excluded that the safety profile of pegcetacoplan in the pivotal study has been minimised. If the important potential risks commonly occur after any authorisation then the additional toxicity could be much greater.

In addition, taking into account of the small sample size of both groups of treatment (pegcetacoplan or eculizumab), interpretation of the safety differences between both groups can be only done with caution as the variability is non-negligible. Identifying a robust signal from a limited data source seems difficult. Full safety results for Study APL2-302, compiling data across all periods of the study are needed.

Infections reported during the pivotal study could be an illustration of that. Indeed, although the risk of serious infections due to encapsulated bacteria is expected with complement inhibitors treatment, none was observed throughout the pivotal study and through all studies in which patients were exposed to systemic pegcetacoplan through the data cut-off date. However, taking into account prior experience of PNH patients treated with C5 inhibitors and review of published data describing the risk of infection in patients with congenital complement deficiencies, the risk of these type of serious infections could not be excluded.

The underlying disease is a confounding factor as it is strongly contributing to the overall reporting of AEs in both treatment arms. Haemolysis, fatigue, headache, abdominal pain and back pain are indeed part of the symptoms of paroxysmal nocturnal haemoglobinuria.

There are uncertainties regarding immunogenicity testing method from the PK point of view that preclude conclusions on immunogenicity of pegcetacoplan. Moreover, the clinical results related to immunogenicty providing from the pivotal study are still not sufficient and it will be monitored further in the PASS.

C5-inhibitors have an important potential risk of malignancies and haematological abnormalities. Although the PD properties are somewhat different, it is not anticipated that the risks would be different. It is deemed that those risks cannot be excluded, and the Applicant agreed to include malignancies and haematological abnormalities as an important potential risk.

There are uncertainties regarding long-term PEG accumulation effects.

Patients with PNH-associated bone marrow failure (including aplastic anaemia PNH, myelodysplastic syndrome) that were not included in the pivotal study have a higher risk of serious infections due to neutropenia according to literature. The safety profile related to these patients is thus for the time being uncertain and the risk of serious infections could be seriously increased in case of any administration to these patients. Patients starting treatment with bone marrow failure are thus considered as missing information in the RMP.

A PASS using registry data, study APL2- 302 and study 307 will investigate the important potential risk of serious hypersensitivity reactions, intravascular haemolysis after drug discontinuation, immunogenicity, malignancies and haematologic abnormalities and potential long-term effects of PEG accumulation

There are no data on use of pegcetacoplan in children, during pregnancy and breastfeeding (except for one case of pregnancy that was reported in Study CP0514, Cohort 4 with no adverse effect on pregnancy, mother or child). A PASS using registry data will evaluate data on pregnancy outcomes.

Experience with pegcetacoplan in Study APL2-302 in elderly subjects >65 years is limited to 17 patients (21.3%). Although there were no apparent age-related differences observed in PK studies, the number of patients aged 65 years and over is not sufficient to determine whether they respond differently from younger patients.

There are no available clinical data for the use of pegcetacoplan in patients with end stage renal disease (ESRD) requiring haemodialysis. Nonclinical findings with potential to affect clinical use included renal findings (renal tubular vacuolation), which were seen in repeat-dose primate studies, might be shown in clinical setting.

PNH patients with body weight below 50 kg are predicted to have up to 34% higher exposure compared to a reference 70 kg subject. Although not many patients with body weight <50 kg are expected in clinical practice, the impact on safety of this increase in exposure is not known.

At the time of planning Study 302, eculizumab was the only approved therapy for PNH. Since July 2019 another C5 inhibitor (ravulizumab) is approved for the treatment of patients with PNH. Since eculizumab and ravulizumab share the same mechanism of action, it is acceptable to view the comparator in this study (eculizumab) as representing both available C5 inhibitors. Rigorous cardiac eligibility criteria and monitoring were implemented to discharge unanticipated cardiac risk.

Table 47: Effects Table for Pegcetacoplan in the treatment of PNH in adult patients that have previously received standard therapy haemoglobinuria (data cut-off: 24 December 2019).

Effect	Short Description	Unit	Pegcetacoplan	Eculzumab	Uncertainties/ Strength of evidence	References
Favourable Effects						
CFB to Week 16 in Hb level	Least-square (LS) mean ± SE	g/dl	2.37 ± 0.363	-1.47 ± 0.666	P<0.0001; primary endpoint was reached	RCP
Transfusion avoidance	proportion of subjects	%	85.4	15.4	Risk difference: 0.6253	RCP

Effect	Short Description	Unit	Pegcetacoplan	Eculzumab	Uncertainties/ Strength of evidence	References
CFB to Week 16 in ARC	LS mean ± SE	109 cells/L	-135.82 ± 6.543	27.79 ± 11.859	P<0.0001; key secondary endpoint	RCP
CFB to Week 16 in LDH	LS mean ± SE	U/L	-14.76 ± 42.708	-10.12 ± 71.025	P=0.9557; key secondary endpoint	RCP
CFB to Week 16 in FACIT-Fatigue Scale score	LS mean ± SE		9.22 ± 1.607	-2.65 ± 2.821	Not tested; key secondary endpoints were tested in a hierarchical manner.	RCP
Unfavourable Effects						
Diarrhoea	Incidence of diarrhoea	n (%)	9 (22.0)	1 (2.6)		RCP
All injection site reactions	Incidence of ISRs	n (%)	15 (36.6)	2 (5.1)	All injection site reactions taken together, in eculizumab they were 2 vaccination site pain	
Injection site erythema	Incidence of injection site erythema	n (%)	7 (17.1)	0		RCP
Injection site reaction	Incidence of injection site reaction	n (%)	5 (12.2)	0		RCP
Injection site swelling	Incidence of injection site swelling	n (%)	4 (9.8)	0		RCP
Abdominal pain	Incidence of abdominal pain	n (%)	5 (12.2)	4 (10.3)		RCP
Infections and infestations	Incidence of infections and infestations	n (%)	12 (29.3)	10 (25.6)	All infections taken together because different types of infection were observed in 1 or 2 patients each	RCP
Haemolysis	Incidence of haemolysis	n (%)	4 (9.8)	9 (23.1)		RCP

Abbreviations: RCP=Randomized control period

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Study APL2-302 is a randomized, controlled, global Phase 3 trial designed to compare the clinical efficacy of pegcetacoplan with a representative C5 inhibitor, eculizumab. The primary endpoint (CFB in Hb level) has been reached in this superiority trial. The following key secondary endpoints: transfusion avoidance, CFB in ARC level and CFB in FACIT-Fatigue score were consistent with the primary analysis. Key secondary endpoints were tested first for non-inferiority and, if all were met, then superiority was tested sequentially for transfusion avoidance, ARC, LDH, and FACIT-Fatigue score using a closed-testing procedure at a significance level of 0.05. CFB in LDH level did not meet non-inferiority by the prespecified analysis. However, a greater percentage of subjects on pegcetacoplan achieved LDH normalization, as compared with eculizumab. With respect to the available information, pegcetacoplan adds a mild

additional toxicity to the target population treated with the proposed dose regimen of 1080 mg twice weekly subcutaneous infusion. It was noted that the treatment effect on the primary endpoint is quite clear at 16-weeks; however, the there is a need to be re-assured of the long-term effect of pegcetacoplan. The applicant submitted efficacy and safety data from the Study APL2-302 open-label period (OLP) from Week 17 through Week 48 + follow-up with a data cut-off date of 23 September 2020. 77 patients were enrolled, completed the Week 48 visit and had either entered follow-up or the extension study, Study APL2-307. Results of the key efficacy analyses of the OLP confirm the results observed during the 16-week RCP.

The amended indication reflects the studied population of PNH patients anaemic despite current treatment with a C5 inhibitor.

From a safety point of view, the main issue is that there is a limited database in terms of number of PNH patients exposed and in terms of duration of exposure, especially in setting of concerned indication with chronic use. The most prominent adverse events were diarrhoea and various infusion site reactions that were observed in much higher frequencies in pegcetacoplan group compared to eculizumab group in randomised controlled portion of the pivotal study. Number of discontinuations was not negligible, with clinically significant events of haemolysis that led to pegcetacoplan or study discontinuation. Immunogenicity has been added as an important potential risk in the updated EU RMP and has been included as a safety concern to be monitored in the PASS. Serious infections have been added as important potential risk in the RMP with additional risk mitigation measure using registry data. Malignancies and haematological abnormalities are also added as important potential risk in the RMP. Additional long-term safety data are still needed to better characterise the safety profile of pegcetacoplan (added as missing information in the RMP).

Long-term PEG accumulation has been added as an important potential risk in the RMP as requested and an endpoint to monitor this potential risk has been added to the post-authorisation safety study (PASS) using the International PNH Interest Group (IPIG) registry.

A PASS using registry data, study APL2- 302 and study 307 will investigate the important potential risk of serious hypersensitivity reactions, intravascular haemolysis after drug discontinuation, immunogenicity, malignancies and haematologic abnormalities and potential long-term effects of PEG accumulation

3.6.2. Balance of benefits and risks

The submitted data show clinically important benefits of pegcetacoplan in patients not adequately controlled by eculizumab, in improved Hb levels and a reduction in transfusion after 16 weeks of treatment. Pegcetacoplan is administered subcutaneously, offering patients a possibility of self-administration that is unavailable with a C5 inhibitor. In the context of a life-long treatment, this is an important aspect from the patient's perspective.

Overall, the safety profile of pegcetacoplan in C5i-treated PNH patients is not so significantly different to that of eculizumab.

3.6.3. Additional considerations on the benefit-risk balance

N/A

3.7. Conclusions

The overall benefit/risk balance of Aspaveli is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Aspaveli is favourable in the following indication:

Treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regards to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Aspaveli in each Member State, the MAH must agree about the content and format of the educational and controlled distribution programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational and controlled distribution programme is aimed at:

- Ensuring that Aspaveli is only dispensed after confirmation that patients received vaccinations against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* or broad-spectrum prophylactic antibiotics.
- Ensuring prescribers or pharmacists receive annual reminders of mandatory revaccinations.
- Providing information about the signs and symptoms of serious infections to healthcare providers and ensure that patients who experience symptoms seek emergency medical treatment.
- Ensuring that prescribers provide patients with the package leaflet and patient card.
- Educate prescribers and patients about the risk of intravascular haemolysis after medicinal product discontinuation and postponement of administration.
- Educate prescribers about the risk of potential long-term effects of PEG accumulation and the recommendation to monitor as clinically indicated, including through laboratory testing.

The MAH shall ensure that in each Member State where Aspaveli is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Aspaveli have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

- **Physician educational material:**
  - Summary of Product Characteristics
  - Guide for healthcare professionals
  - Patient card

  - **Guide for healthcare professionals:**
    - Treatment with Aspaveli may increase the risk of serious infections with encapsulated bacteria.
    - The need for patients to be vaccinated against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* and/or receive antibiotic prophylaxis.
    - Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines).

- Risk of intravascular haemolysis after drug discontinuation and postponement of administration, its criteria, the required post-treatment monitoring, and its proposed management.
- Risk of potential long-term effects of PEG accumulation and the recommendation to monitor as clinically indicated, including through laboratory testing.
- The need to educate patients/carers of the following:
    - the risks of treatment with Aspaveli
    - signs and symptoms of serious infections, hypersensitivity reactions, and what action to take
    - the patient/carer guides and its content
    - the need to carry the patient card and to tell any healthcare practitioner that he/she is receiving treatment with Aspaveli
    - the requirement for vaccinations/antibiotic prophylaxis
    - the enrolment in the post-authorisation safety study (PASS)
- Instructions on how to handle possible adverse events (AEs).
- Information about the PASS, the importance of contributing to such a study, and how to enter patients.
- Remarks on the importance of reporting on specific adverse reactions, namely: serious infections, serious hypersensitivity reactions, and risk of intravascular haemolysis after medicinal product discontinuation.

- **Patient card:**
    - A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Aspaveli.
    - Signs or symptoms of the serious infections and warning to seek immediate attention from a healthcare professional if above is present.
    - Contact details of the Aspaveli prescriber.

The patient information pack:

- Patient information leaflet
- Patient/carer guide

- **Patient/carer guide:**
    - Treatment with Aspaveli may increase the risk of serious infections with encapsulated bacteria, serious hypersensitivity reactions, and risk of intravascular haemolysis after medicinal product discontinuation.

- A description of the signs and symptoms of serious infections, hypersensitivity reactions, intravascular haemolysis after medicinal product discontinuation, and the need to seek emergency care at the nearest hospital.
- The importance of vaccination prior to treatment with Aspaveli and/or to receive antibiotic prophylaxis.
- Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines).
- Detailed description of the modalities used for the self-administration of Aspaveli.
- Recommendation for use of effective contraception in women of childbearing potential.
- Remarks on the importance of reporting on specific adverse reactions, namely: serious infections, serious hypersensitivity reactions, and risk of intravascular haemolysis after medicinal product discontinuation.
- Instructions on how to view the patient self-treatment video on any internet-connected device.
- Enrolment in the PASS.

The MAH shall send annually to prescribers or pharmacists who prescribe/dispense Aspaveli, a reminder in order that the prescriber/pharmacist checks if a re-vaccination against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* is required for his/her patients on treatment with Aspaveli, in accordance with national vaccination guidelines.

The MAH shall ensure that in each Member State where Aspaveli is marketed, a system aimed to control distribution beyond the level of routine risk minimisation measures is in place. The following requirement needs to be fulfilled before the product is dispensed: Submission of written confirmation of the patient's vaccination against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* and/or prophylactic antibiotic treatment according to national vaccination guidelines.

Conditions or restrictions with regards to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that pegcetacoplan is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.