CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215014Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	NDA 215014
Priority or standard	Priority
Submit date(s)	9/14/2020
Received date(s)	9/14/2020
PDUFA goal date	5/14/2021
Division/office	Division of Nonmalignant Hematology (DNH)
Review completion date	4/2/2021
Established/proper name	pegcetacoplan
(Proposed) proprietary name	Empaveli
Pharmacologic class	Complement inhibitor
Code name	N/A
Applicant	Apellis Pharmaceuticals
Dosage form(s)/formulation(s)	Solution for infusion
Dosing regimen	Subcutaneous twice weekly
Applicant proposed indication(s)/ population(s)	Treatment of adult patients with paroxysmal nocturnal hemoglobinuria
Proposed SNOMED indication	Paroxysmal nocturnal hemoglobinuria disorder
Regulatory action	Approval
Approved dosage (if applicable)	1080 mg/20 mL (54 mg/mL)
Approved indication(s)/ population(s) (if applicable)	Treatment of adult patients with paroxysmal nocturnal hemoglobinuria
Approved SNOMED term for indication (if applicable)	Click or tap here to enter text.

Abbreviations: NDA, new drug application; PDUFA, Prescription Drug User Fee Act; SNOMED, Systemized Nomenclature of Medicine

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Glossary

ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
APL-2	pegcetacoplan
ARC	absolute reticulocyte count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BD	birth day
BIW	twice a week
BW	body weight
C	complement protein
CD	cluster of differentiation
CFB	change from baseline
CI	confidence interval
CL	clearance
COVID-19	coronavirus disease-2019
CrCl	creatinine clearance
CT	computed tomography
CYP	cytochrome P450
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
E_{max}	maximum proportional change from baseline
ePPND	enhanced pre- and post-natal development
E-R	exposure-response
ETA	estimate of interindividual variability
EVH	extravascular hemolysis
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
GD	gestation day
GOF	goodness-of-fit
GPI	glycosylphosphatidylinositol
Hb	hemoglobin
IC_{50}	half-maximal inhibitory concentration
IIV	interindividual variability
ITT	intent-to-treat
IV	intravenous
IVH	intravascular hemolysis
LDH	lactate dehydrogenase
LSM	least squares mean
MAC	membrane attack complex
MAS	macrophage activation syndrome
MNAR	missing not at random
NDA	new drug application

NIM	noninferiority margin
NOAEL	no observed adverse effect level
OAT	organic anion transporter
OCT	organic cation transporter
PD	pharmacodynamic
PEG	polyethylene glycol
PEG-40	40-kilodalton polyethylene glycol
P-gp	P-glycoprotein
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
PNH	paroxysmal nocturnal hemoglobinuria
PopPK	population PK
PPD	postpartum day
PRBC	packed red blood cell
PT	preferred term
QTc	corrected QT interval
RBC	red blood cell
RCP	randomized control period
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
TEAE	treatment-emergent adverse event
TK	toxicokinetic
T_{max}	time to maximum concentration
V2	apparent volume
V_d	volume of distribution
VPC	visual predictive check

I. Executive Summary

1. Summary of Regulatory Action

On September 14, 2020, Apellis Pharmaceuticals submitted an original New Drug Application for Empaveli (pegcetacoplan) for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). Pegcetacoplan is a complement inhibitor composed of two identical pentadecapeptides covalently bound to the ends of a linear 40 kDa polyethylene glycol molecule. Pegcetacoplan binds to complement protein (C) 3 and its activation fragment C3b, thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation.

The review team recommends approval of pegcetacoplan (Empaveli) for the treatment of adult patients with PNH.

Overview of PNH and Current Treatment Options

PNH is a rare, chronic and life-threatening disease characterized by somatic mutation in the X-linked phosphatidylinositol glycan class A gene. Loss of functional phosphatidylinositol glycan class A leads to deficiency in glycosyl phosphatidylinositol (GPI)-anchored proteins, which prevent red blood cells (RBCs) from anchoring the complement regulatory proteins cluster of differentiation (CD) 55 and CD59, leading to chronic intravascular hemolysis (IVH) with recurrent exacerbations, anemia, smooth muscle dystonia, and a high risk of thrombosis often in atypical locations. Classical PNH presents predominately with hemolytic anemia without overt bone marrow failure, although it can also manifest with marrow failure. Prior to the availability of a specific therapies, PNH resulted in the death of approximately half of affected individuals, usually due to thrombotic complications.

The approach to therapy depends on severity of symptoms and degree of hemolysis. For patients with hemolytic PNH, allogeneic hematopoietic cell transplantation and complement inhibition with complement inhibitors are the only established therapies. Supportive therapy includes RBC (RBC) transfusions, supplemental iron, and folic acid. Two anticomplement therapies are approved by the Food and Drug Administration: eculizumab and ravulizumab-cwvz. Eculizumab is a humanized monoclonal antibody that binds to C5 and prevents its cleavage to C5a and C5b, which is required for formation of the membrane attack complex (MAC). RBCs are normally protected from MAC formation by the GPI-anchored cell-surface protein CD59; the PNH RBCs lacking CD59 are susceptible to MAC formation. Eculizumab interferes with this step and reduces IVH. Ravulizumab-cwvz is a monoclonal antibody that also binds to C5 and prevents cleavage of C5 by C5 convertase. Ravulizumab-cwvz is similar to eculizumab with regard to efficacy and toxicity but has a longer half-life, which permits maintenance therapy every 8 weeks.

In addition to IVH mediated by MAC, RBCs undergo complement-mediated extravascular hemolysis (EVH) in PNH. The mechanism of EVH is macrophage destruction of RBCs opsonized with C3 fragments such as C3d. EVH is normally prevented by the GPI-anchored

protein CD55, which is also missing from PNH RBCs. Binding of C3 fragments is not prevented by C5 inhibitors. Some patients receiving C5 inhibitor therapy may develop or have unmasked EVH characterized by mild to moderate anemia and a positive direct antiglobulin test for C3d.

In PNH, EVH is facilitated by C3b opsonization whereas IVH is mediated by the downstream membrane attack complex (MAC). Pegcetacoplan acts proximally in the complement cascade controlling both C3b-mediated EVH and terminal complement-mediated IVH.

Design of Study APL-302

In support of the proposed indication, the Applicant conducted Study APL-302 in patients with PNH. Study APL2-302 was a Phase 3, prospective randomized, multicenter, open-label, active comparator-controlled study in which 80 adult subjects were randomized 1:1 to pegcetacoplan 1,080 mg twice a week or every 3 days if clinically indicated or their current dosage of eculizumab. The trial consisted of a 4-week run-in period, a 16-week randomized treatment period, and a 32-week open-label period, which is ongoing. All patients who completed the 48-week total treatment period were eligible to enroll in a separate long-term extension study. The primary endpoint of the study was demonstration of superiority of pegcetacoplan to eculizumab monotherapy in subjects with PNH currently on treatment with eculizumab as measured by change from baseline (CFB) in hemoglobin (Hb) level at Week 16. Baseline was defined as the average of measurements recorded prior to taking the first dose of study drug. The between-treatment group comparison was performed using the mixed model for repeated measures under the assumption that data were missing at random. Randomization was stratified by the number of packed RBC transfusions within the 12 months prior to Day -28 (<4; ≥4) and platelet count at screening (<100,000/mm^3; ≥1000,000/mm^3). In this population, transfusions were expected and the protocol included prespecified criteria allowing subjects to receive necessary packed RBC transfusions during the run-in period (Day -28 to <Day 1) and the randomized control period (Day 1 to Week 16) if Hb was <7 g/dL without symptoms or <9 g/dL with symptoms.

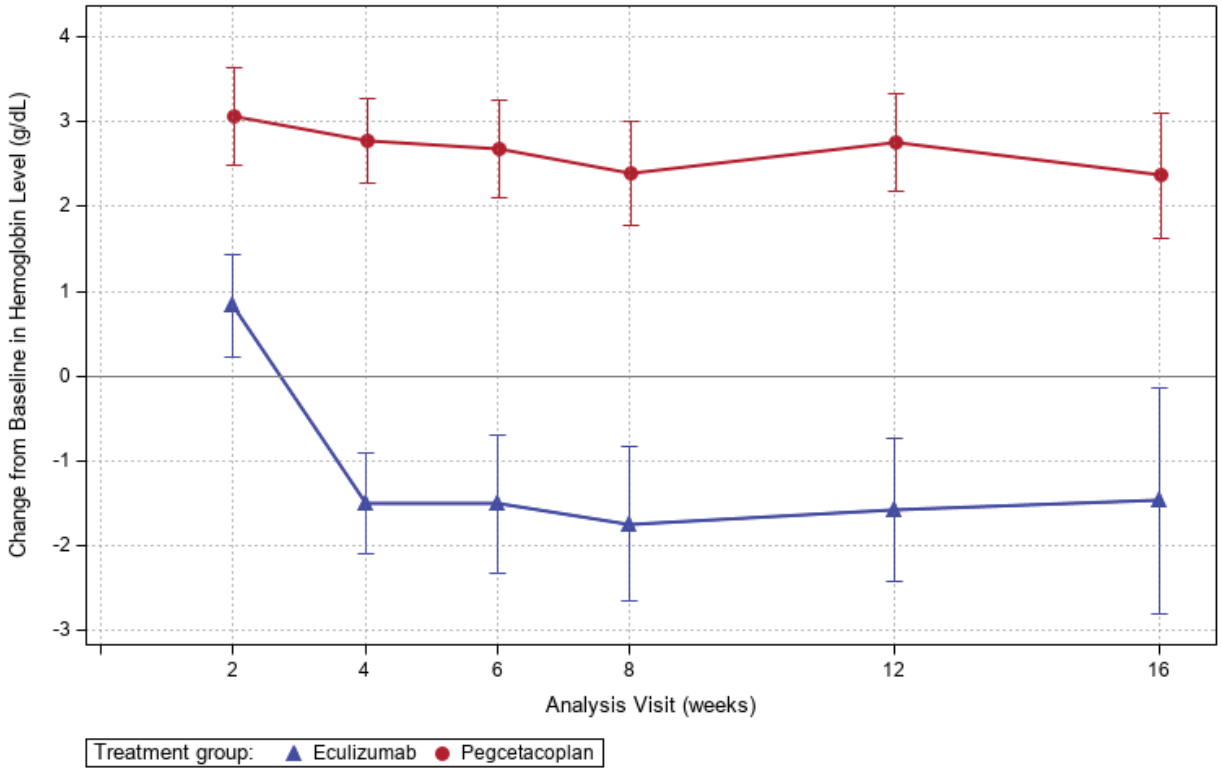
Efficacy

Study APL-302 demonstrated a statistically significant effect on its primary endpoint, CFB in Hb levels ($p<0.0001$). The adjusted least squares mean (LSM) CFB in Hb level was 2.4 g/dL in the pegcetacoplan group and -1.5 g/dL in the eculizumab group, for a mean difference between treatments of 3.8 g/dL (95% confidence interval [CI] 2.33 to 5.34) at Week 16 (Figure 1). Sensitivity analyses using the pattern mixture model and tipping point model were conducted to address the occurrence of missing Hb data at Week 16. These sensitivity analyses demonstrated that the primary endpoint analysis results were robust to alternate scenarios for missing data assumptions.

Noninferiority was demonstrated in the endpoints of transfusion avoidance, defined as the proportion of patients that did not require a transfusion during the randomized control period and CFB in absolute reticulocyte count. In the pegcetacoplan group, 35 subjects (85%) achieved transfusion avoidance, compared to 6 subjects (15%) in the eculizumab group, for a treatment difference of 63 (95% CI 48 to 77).

The adjusted LSM for the CFB in reticulocytes (10^9/L) was -136 (standard deviation [SD] 6.5) in the pegcetacoplan group, compared to 28 (SD 11.9) in the eculizumab group, for a treatment difference of -164 (95% CI -189.9 to -137.3).

Figure 1. Mean CFB in Hb Level During RCP by Visit and Treatment Group, ITT Population, APL2-302



Note: Treatment effect estimates from a mixed model are shown.
Note: The mixed model contained the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.
Note: Vertical lines represent 95% confidence intervals for least squares mean estimates.

Source: Statistical reviewer's analysis.
Abbreviations: CFB, change from baseline; Hb, hemoglobin; ITT, intent-to-treat; RCP, randomized control period

Noninferiority was not met for CFB in lactate dehydrogenase (LDH). Noninferiority was not assessed for Functional Assessment of Chronic Illness Therapy–Fatigue score because of the break in the prespecified hierarchical testing order.

During the run-in period, all subjects had an increase in Hb when receiving both eculizumab and pegcetacoplan. At the beginning of the RCP, serum Hb decreased in the eculizumab group as pegcetacoplan was discontinued. This decline (a mean decrease in excess of 2 g/dL between Weeks 2 and 4) was accompanied by increases in LDH and C3 deposition on erythrocytes, particularly Type III RBCs, consistent with hemolysis. Although the evidence is not conclusive, it is quite possible that discontinuation of pegcetacoplan resulted in the unmasking of the C3 opsonization, with resultant extravascular hemolysis. By week 4 of the RCP, the eculizumab group had hemoglobin, LDH and C3 deposition results trending toward baseline levels.

Demographics and baseline disease characteristics were generally well balanced between treatment groups. The mean age was 50.2 (SD 16.3) years in the pegcetacoplan group and 47.3 (SD 15.8) years in the eculizumab group and 65.9% of subjects were female. The mean baseline

Hb level was 8.7 g/dL (SD 1.1) in the pegcetacoplan group and 8.7 g/dL (SD 0.9) in the eculizumab group. A total of 38 patients in the pegcetacoplan group and 39 patients in the eculizumab group completed the 16-week randomized control period and continued to the 32-week open-label period.

The pharmacodynamic data (PNH RBC clone size and C3 deposition on PNH RBCs) provide mechanistic support of the efficacy findings. The mean reduction of C3 deposition on Type II and III PNH RBCs (CFB to Week 16) was -17.94% in the pegcetacoplan group and -3.16% in the eculizumab group) provides evidence that pegcetacoplan protects PNH RBCs from EVH by decreasing opsonization of RBCs. The mean PNH RBC clone size (TYPE III) in the pegcetacoplan group increased from 47% at baseline to 91% at Week 16, compared to a 50% mean PNH clone size at baseline that decreased to 46% at Week 16 in the eculizumab group. In summary, the observed changes in pharmacodynamic biomarkers, including serum C3 levels, proportion of PNH Type II and III RBCs, and C3 deposition on RBCs, support its mechanism of action and provide mechanistic evidence for pegcetacoplan as an effective treatment for PNH.

Because APL-302 only studied patients who had received eculizumab, a key review issue was whether the application supported the proposed broad indication for treatment of adult patients with PNH (previously treated with eculizumab and eculizumab-naïve). The results of Study APL-302 are supported by two uncontrolled studies in patients with PNH who were complement inhibitor-naïve: Studies APL2-202 and APL2-C-PNH-204. These studies enrolled a total of 24 patients with PNH who had a PNH clone size of at least 10%, an LDH at least two-fold the upper limit of normal, and at least one transfusion in the 12 months prior to enrollment. In both studies, treatment duration was approximately 1 year. Increases in Hb were observed and the results were consistent with those of Study APL-202. In Study APL2-204, the mean Hb value was 11.85 g/dL at Week 16 (Day 113) with a mean CFB of 3.46 g/dL; in Study APL2-202, the mean Hb value was 12.6 g/dL at Week 16 with a mean CFB of 4.87 g/dL. These Hb levels continued to increase from baseline to Day 365 in Studies APL2-204 and APL2-202, with mean Hb values of 12.4 g/dL and 13.0 g/dL at Day 365 in Studies APL2-204 and APL2-202, respectively.

Further support for the broad indication comes from exposure-response (E-R) analyses of Studies APL2-204 and APL2-202 as well as in nine eculizumab-treated subjects in Study CP0514, in which trough pegcetacoplan concentrations and time-matched Hb levels were measured weekly or every 2 weeks throughout the trials. The pharmacokinetic and efficacy data (Hb and LDH) from these four studies were used for E-R analysis of the Hb and LDH response with time-matched pegcetacoplan concentrations.

The E-R analysis for Hb response estimated that the maximal proportional change in Hb is a 36.3% increase from baseline and the pegcetacoplan concentration corresponding to half of the maximal effect is 272 μg/mL. Prior eculizumab treatment did not affect the maximal proportional change of the Hb response or the half-maximal effective concentration. Predicted steady-state Hb levels were similar for eculizumab-treated and eculizumab-naïve subjects, with a mean ratio of 1.07 (90% CI 0.997 to 1.14). Therefore, the E-R analysis suggests that the Hb response to pegcetacoplan is not affected by prior eculizumab treatment.

The E-R relationships for LDH response were different between the eculizumab-treated and eculizumab-naïve patients, mainly due to their different LDH levels at baseline. Nonetheless, at steady state following the proposed dose of pegcetacoplan, LDH levels are predicted to decrease to 231 IU/L in naïve patients, a change comparable to that in eculizumab-treated patients. At the

proposed dose, pegcetacoplan exposures are expected to achieve close to the maximal effect on LDH control for both eculizumab-naïve and -experienced patients with PNH.

Safety

The safety database is limited, as would be expected given the size of the affected population. The most common adverse reactions were injection site reactions and infections, diarrhea, abdominal pain, respiratory tract infections, viral infections, and fatigue. All the events were generally mild.

The mechanism of action of pegcetacoplan is proximal inhibition of the complement system, which creates an increased risk of serious infections caused by encapsulated bacteria, including *Streptococcus pneumoniae, Hemophilus influenzae*, and *Neisseria meningitidis*. Thus, major potential risks explored in the clinical safety data include serious infections caused by encapsulated bacteria and infusion-related reactions. The mechanism of action of pegcetacoplan is proximal inhibition of the complement system, which creates an increased risk of serious infections caused by encapsulated bacteria, including *S. pneumoniae, H. influenzae*, and *N. meningitidis*. These associations are based on a review of manifestations of inherited C3 deficiencies, which have shown recurrent and severe infections involving the respiratory system, meninges, and bloodstream caused by the above-mentioned encapsulated bacteria. There have been no reports of meningococcal infection or other severe infections potentially related to encapsulated bacteria up to the data cutoff date.

Additional risks include systemic hypersensitivity reactions (e.g., facial swelling, rash, urticaria) and events, mostly mild, which have occurred in patients receiving pegcetacoplan. Additional risks include the development of serious hemolysis after discontinuation of pegcetacoplan, and the labeling information provides management recommendations if treatment needs to be suspended or discontinued.

Conclusion

In this rare disease with a limited patient population, the findings in Study APL-302, an adequate and well controlled study, along with confirmatory evidence from two independent studies, Studies APL2-204 and APL2-202 in subjects who are C5 inhibitor-naïve, provide substantial evidence of effectiveness for pegcetacoplan for the proposed indication. There is evidence of sustained efficacy in the supportive studies, providing evidence for durability of response. The safety database, though limited in size, does not raise significant safety concerns. The potential risk of serious infections caused by encapsulated organisms can be mitigated via labeling, a boxed warning, and a risk evaluation and mitigation strategy. The data provide substantial evidence of a clinical benefit that outweighs the risks and therefore the application warrants approval. The approval will include a postmarketing requirement to conduct a registry to further characterize the long-term safety of pegcetacoplan.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, chronic, and life-threatening disease characterized by uncontrolled complement activation leading to hemolytic anemia, thromboembolism, bone marrow failure, and systemic complications. The disease is caused by an absence of complement inhibitor proteins CD55 and CD59 on red blood cell (RBC) surfaces, resulting in continuous activation of the alternative complement pathway and chronic hemolysis in both the intravascular and extravascular compartments by activation of the C5-dependent terminal membrane attack complex (MAC) and C3 opsonization of RBCs. • PNH causes significant morbidity and mortality, including thromboembolism, pulmonary hypertension, and end-organ damage. The reported median survival prior to the availability of specific therapies was 10 to 22 years. Patients with PNH have a diminished quality of life secondary to their morbidities.	• PNH is a serious, life-threatening disease with significant morbidity and mortality. • PNH is a chronic disease that requires lifelong treatment.
Current Treatment Options	• Current treatment options for patients with PNH include pharmacological therapies and allogeneic bone marrow transplantation. FDA-approved pharmacological therapies include: – Eculizumab (Soliris®), a humanized monoclonal antibody targeting the complement protein (C5) of the terminal complement cascade that was approved in 2007. Dosing is weekly for 4 weeks followed by maintenance dosing every 2 weeks.	• These two drugs target C5-dependent intravascular hemolysis. C3 binding and subsequent extravascular hemolysis may occur as the RBCs bound with C3 are no longer lysed by the terminal complement pathway. As a result, these drugs mainly decrease IVH, with minimal effect on EVH. • There is a continued unmet medical need for alternative treatment options for PNH that control hemolysis in both the intravascular and extravascular compartments.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	– A second C5 inhibitor therapy, ravulizumab-cwvz (ULTOMIRIS®), is a long-acting derivative of eculizumab that binds to C5 complement with high affinity, preventing generation of the terminal complement complex. Ravulizumab-cwvz was approved in 2018 for adult patients with PNH. Dosing is a loading dose followed by every 8-week maintenance dosing starting 2 weeks after loading dose administration.	
Benefit	• The effectiveness of pegcetacoplan was evaluated in APL2-302, an adequate and well controlled trial. Study APL2-302 was a randomized, open-label, active-comparator trial in 80 adult patients with PNH receiving eculizumab with continued hemoglobin (Hb) levels <10.5 g/dL. Patients were enrolled in a 4-week run-in period with coadministration of pegcetacoplan and eculizumab followed by a 16-week randomized control period (RCP) where patients received monotherapy of either pegcetacoplan 1,080 mg SC infusion twice weekly (or three times weekly) or their current dosage of eculizumab therapy. • Study APL-302 demonstrated a statistically significant effect on the primary endpoint, CFB in Hb level ($p<0.0001$). The adjusted mean CFB in Hb level was 2.4 g/dL in the pegcetacoplan group versus -1.5 g/dL in the eculizumab group, demonstrating an adjusted mean increase of 3.8 g/dL with pegcetacoplan compared to eculizumab at Week 16 (95% confidence interval [CI], 2.33-5.34 g/dL). • Noninferiority was demonstrated in the endpoint of transfusion avoidance defined as the proportion of patients who did not require a transfusion during the RCP and CFB in absolute reticulocyte count. In the pegcetacoplan group, 35 subjects (85%) achieved transfusion avoidance, compared to 6 (15%) in the eculizumab group; a treatment difference of 63% (95% CI 48-77%). The adjusted least squares mean (SD) for the CFB in reticulocytes (10^9/L) was -136 (SD 6.5) in the pegcetacoplan group compared to 28 (SD 11.9) in the eculizumab group; a treatment difference of -164 (95% CI -189.9 to -137.3).	• Study APL2-302 demonstrated the superiority of pegcetacoplan compared to eculizumab in improving Hb levels in adult patients with PNH receiving eculizumab with continued Hb levels <10.5 g/dL.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Pegcetacoplan's treatment effect was generally consistent across subgroups based on demographics and clinical characteristics.	
Risk and Risk Management	• An important risk associated with C3 inhibition is increased susceptibility to serious infections caused by encapsulated bacteria including *Streptococcus pneumoniae, Hemophilus influenzae,* and *Neisseria meningitidis*. In the Phase 3 trial and three supportive PNH trials, no patients have experienced a serious infection due to encapsulated bacteria as of the data cutoff. • In the primary safety population of Study APL2-302, no deaths occurred during the run-in period or RCP. • The most commonly reported treatment-emergent adverse reactions (>5%) in the 39 patients treated with pegcetacoplan monotherapy during the RCP were injection site reactions, infections, diarrhea, and abdominal pain. Most AEs were Grade 1 or Grade 2 in severity. • There is a theoretical risk of development of autoimmune disease associated with C3 deficiency. To understand this long-term risk, a postmarketing requirement will be issued to complete ongoing studies	• Overall, the safety profile of pegcetacoplan is acceptable for the proposed indication, with the biggest risk being serious infection caused by encapsulated bacteria. • To mitigate the risk of serious infections caused by encapsulated bacteria, pegcetacoplan will only be available through a restricted program under a risk evaluation and mitigation strategy, under which prescribers must enroll in the program. • Additional mitigation strategies for the risk of serious infections caused by encapsulated bacteria include a boxed warning in the prescribing information, which will include a boxed warning for serious infections caused by encapsulated bacteria, informing providers of the risk and mitigation strategies. • The Prescribing Information will include information to immunize patients with vaccines against encapsulated organisms at least 2 weeks prior to administering the first dose of pegcetacoplan.

Abbreviations: AE, adverse event; C, complement protein; CFB, change from baseline; CI, confidence interval; Hb, hemoglobin; MAC, membrane attack complex; PNH, paroxysmal nocturnal hemoglobinuria; RCP, randomized control period; SD, standard deviation; TEAE, treatment-emergent adverse event

2.2. Conclusions Regarding Benefit-Risk

Study APL-302 demonstrated a statistically significant effect on its primary endpoint, CFB in hemoglobin levels (P<0.0001). The adjusted LSM CFB in Hb level was 2.4 g/dL in the pegcetacoplan group and -1.5 g/dL in the eculizumab group, for a mean difference between treatments of 3.8 g/dL (95% CI 2.33 to 5.34) at Week 16. Pegcetacoplan was noninferior to eculizumab in transfusion avoidance and absolute reticulocyte count. Transfusion avoidance was achieved by 35 of 41 patients (85%) in the pegcetacoplan group and 6 of 39 patients (15%) in the eculizumab group. The adjusted mean CFB to Week 16 in absolute reticulocyte count was -136×10^9/L for the pegcetacoplan group and 28×10^9/L for the eculizumab group. The LSM difference between treatment groups was -164×10^9/L. Pegcetacoplan did not meet noninferiority to eculizumab in CFB to Week 16 in LDH. Noninferiority could not be assessed for the Functional Assessment of Chronic Illness Therapy-Fatigue score because of a lack of statistical significance in the more proximal hierarchical testing scheme.

The safety database is limited, as would be expected given the size of the affected population. The most common adverse reactions were injection site reactions, infections, diarrhea, abdominal pain, respiratory tract infections, viral infections and fatigue. These reactions were generally mild.

The major potential risks include serious infections caused by encapsulated bacteria and infusion-related reactions. The mechanism of action of pegcetacoplan is proximal inhibition of the complement system, which creates an increased risk of serious infections caused by encapsulated bacteria, including *S. pneumoniae, H. influenzae*, and *N. meningitidis*. The hypothetical risk is based on a review of the manifestations of inherited C3 deficiencies, which include recurrent and severe infections involving the respiratory system, meninges, and bloodstream caused by encapsulated bacteria. There have been no reports of meningococcal infection or other severe infections potentially related to encapsulated bacteria up to the data cutoff date. With 80 subjects in the safety database treated for a median duration of 4.6 months, the upper limit of the 95% CI for the risk of such infections is 1/(80/3), or ~4%, based on the "rule of three."

The literature describes a theoretical risk of autoimmunity in patients with inherited C3 deficiency, which will be further addressed in a postmarketing requirement for long-term safety. The benefit-risk profile for pegcetacoplan in the proposed population of adult patients with PNH appears acceptable.

In summary, the clinical benefit of pegcetacoplan for PNH outweighs its known and theoretical risks, justifying the approval of pegcetacoplan for the treatment of adult patients with PNH.

II. Interdisciplinary Assessment

3. Introduction

Pegcetacoplan (proprietary name, Empaveli), a new molecular entity, is a small molecule that acts as a complement protein (C) 3 inhibitor. Pegcetacoplan is a symmetrical molecule composed of two identical pentadecapeptides covalently bound to the ends of a linear 40 kDa polyethylene glycol (PEG, PEG 40). The peptide moieties have high binding affinities for C3, which inhibit activation of C3. The Applicant proposes the following indication: the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

The proposed dosing regimen is 1,080 mg/20 mL (54 mg/mL) in a single-dose vial, which is to be self-administered by subcutaneous (SC) infusion twice a week (BIW) using a commercially available syringe system infusion pump.

Disease Background

PNH is a rare, progressive, and life-threatening disease characterized by uncontrolled complement activation leading to hemolytic anemia (both intravascular and extravascular), peripheral cytopenias, increased susceptibility to thrombosis, and bone marrow dysfunction (Brodsky 2014). The median age of diagnosis is approximately 30 years and approximately 10% of patients are younger than 21 years (Hillmen et al. 1995; Schrezenmeier et al. 2014; Schrezenmeier et al. 2020). The prevalence of PNH is estimated at 15.9 cases per million individuals worldwide (Hill et al. 2006) and the incidence is estimated at 0.1 to 0.2/100,000 persons per year (Devalet et al. 2015).

PNH is characterized by a somatic mutation in the phosphatidylinositol glycan class A gene, leading to the partial or complete absence of certain GPI-anchored proteins. Specifically, PNH is caused by complement-mediated lysis of erythrocyte clones lacking functional surface GPI-anchored complement regulatory proteins, cluster of differentiation (CD) 55 and CD59. This results in erythrocytes that are highly susceptible to the membrane attack complex (MAC) and uncontrolled complement-mediated hemolysis. Uncontrolled complement activation leads to intravascular hemolysis (IVH) mediated by the C5-dependent MAC and extravascular hemolysis (EVH) mediated by accumulation of C3 fragments on red blood cells (RBCs) and C3b opsonization (Risitano et al. 2009; Hill et al. 2019; Brodsky et al. 2021).

The onset of PNH is insidious and the disease is generally chronic and progressive with heterogeneous manifestations. Signs and symptoms include anemia, dyspnea, abdominal pain, extreme fatigue, thrombosis, cytopenias, end-organ damage, smooth muscle dystonias, and bone marrow failure (Sharma 2013; Sahin et al. 2015). Disease exacerbations occur spontaneously or in the setting of infection, trauma, or physical exertion (Sharma 2013). Lactate dehydrogenase (LDH) is used to measure complement-mediated IVH (Parker et al. 2005).

PNH leads to significant morbidity and mortality with ongoing hemolysis and the disease is considered life-threatening (Sahin et al. 2015). Morbidities for patients with PNH include

thromboembolism, pulmonary hypertension, renal and cardiac failure, infection, myelodysplastic syndrome, and aplastic anemia. Thrombotic events account for up to 67% of deaths in patients with PNH, 29 to 44% of whom have at least one thrombosis in their lifetime (Hillmen et al. 1995). Prior to the approval and use of eculizumab (C5 inhibitor), patients with PNH had a median survival of 10 to 22 years (Hillmen et al. 1995). Thrombosis is a common cause of mortality in PNH. These morbidities diminish the quality of life of patients with PNH by causing, for instance, extreme fatigue, chronic pain, abdominal pain, erectile dysfunction, dyspnea, and frequent clinic visits and hospitalizations for transfusions, dialysis, and/or anticoagulation therapy (Hill et al. 2006; Brodsky 2014).

Analysis of Current Treatment Options

Treatment of PNH includes the inhibition of complement activity to block hemolysis and prevent thrombosis. There are currently two approved drugs for PNH—eculizumab (Soliris®) and ravulizumab-cwvz (ULTOMIRIS®). Eculizumab was approved in 2007 for the treatment of adults with PNH and Ravulizumab was approved in 2018 for the same indication.

Prior to the approval of eculizumab, treatment historically was centered around supportive care and prevention of disease complications, including RBC transfusions for anemia (Sahin et al. 2015). Additional management of hemolysis includes corticosteroids, androgen therapy, transfusions, splenectomy, complement inhibitor therapy, and stem cell transplantation (Parker et al. 2005). The most common therapeutic strategies are terminal complement blockade and bone marrow transplantation.

Eculizumab (Soliris®) was approved in 2007 for the treatment of patients with PNH to reduce hemolysis. Eculizumab is a humanized monoclonal antibody that specifically binds to C5, preventing its cleavage into C5a and C5b during complement activation thereby inhibiting the formation of the terminal complement cascade or MAC (Kelly et al. 2009). Eculizumab is administered intravenously weekly for the first 4 weeks followed by a fifth dose 1 week later and dosing every 2 weeks thereafter. At the start of the Applicant's Phase 3 study in June 2018, eculizumab was the only therapy available for the treatment of PNH and was used as the active comparator for Study APL2-302.

Ravulizumab-cwvz (ULTOMIRIS®) is a humanized monoclonal antibody and a terminal C5 inhibitor approved in 2018 for the treatment of adult patients with PNH. Ravulizumab-cwvz is a longer-acting C5 inhibitor therapy and is administered as a loading dose followed by maintenance intravenous (IV) dosing once every 8 weeks. Ravulizumab-cwvz has a four-fold longer mean half-life than eculizumab, providing sustained C5 inhibition over 8-week dosing intervals.

Both eculizumab and ravulizumab-cwvz specifically bind to C5 with high affinity, thereby preventing generation of the terminal complement complex. Consistent with this mechanism of action, they each have been shown to similarly control IVH as monitored by LDH levels. Although approved C5 inhibitor therapies control IVH and have improved the disease trajectory for patients with PNH, certain patients continue to have suboptimal C5 blockade, resulting in a potential risk of continued hemolysis and a sustained risk of thromboembolic events (Kelly et al. 2009; Brodsky 2017). C5 inhibitor therapy can control IVH, but does not prevent EVH, leading to ongoing hemolysis (Risitano et al. 2009; Hill et al. 2010; Risitano et al. 2014). Additionally, approximately 11 to 27% of patients experience breakthrough hemolysis due to suboptimal C5

inhibition with eculizumab (Brodsky et al. 2021). Despite pharmacologic C5 inhibition, low hemoglobin (Hb) levels, elevated reticulocyte counts and bilirubin levels, continued need for RBC transfusions, and persistent patient-reported fatigue are indicators of ongoing disease activity.

Drug Class

Pegcetacoplan is a new molecular entity that belongs to the complement inhibitor class. Pegcetacoplan is a symmetrical molecule composed of two identical pentadecapeptides covalently bound to the ends of a linear PEG-40 molecule. The peptide moieties bind to C3, resulting in proximal inhibition of the complement cascade. Pegcetacoplan was developed in a research and development program by Apellis Pharmaceuticals, Inc. Study APL2-302 was designed to test the clinical hypothesis that by inhibiting C3 and C3b, pegcetacoplan may reduce the occurrence of hemolysis in patients with PNH.

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. Proposed Indication for the Treatment of Adult Patients With PNH: Inclusion of C5 Inhibitor Treatment-Naïve and -Experienced Patients

3.1.1.2. Acceptability of Extending Inclusion Criteria to Include Patients Treated With Any Approved C5 Inhibitor Therapies

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Risk of Serious Infection Caused by Encapsulated Bacteria

3.1.2.2. Theoretical Increased Risk of Autoimmune Disease Development With C3 Deficiency

3.2. Approach to the Review

This is a joint review. Sara Jimenez and Yeh-Fong Chen focused on the data supporting efficacy. The Clinical Data Scientist team (Qunshu Zhang and Jinzhong Liu) focused on the data supporting safety and efficacy. Julie Weisman and Tanya Wroblewski focused on the data supporting safety. Fred Alavi and Todd Bourcier reviewed the nonclinical toxicology studies, and Li Li and Sudharshan Hariharan reviewed the clinical pharmacology data. Table 3 provides an overview of the clinical trials submitted in support of the efficacy and/or safety determinations for pegcetacoplan.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Pegcetacoplan

Trial Identifier	Trial Population	Trial Design	Treatment Dosing	Treatment Duration	Primary Objectives	Sample Size	Status
APL2-302	C5 inhibitor-experienced adult subjects with PNH	Phase 3, open-label, active-comparator controlled study	Pegcetacoplan 1,080 mg SC twice weekly or current dose of eculizumab for 16 weeks	Run-in period: 4 weeks RCP: 16 weeks Open-label: 32 weeks	To establish the safety and efficacy of pegcetacoplan compared to eculizumab in subjects with PNH who continue to have hemoglobin (Hb) levels <10.5 g/dL despite treatment with eculizumab	80 subjects Pegcetacoplan: 41 subjects Eculizumab: 39 subjects	RCP: Completed Open-label: Ongoing
APL2-202	C5 inhibitor-naïve adult subjects with PNH	Open-label, randomized, multi-ascending dose study	Pegcetacoplan 270 to 360 mg/day SC	Up to 1 year	To assess the safety, tolerability, efficacy and PK of multiple SC doses of pegcetacoplan in subjects with PNH who have no received treatment with eculizumab in the past	4 subjects	Completed
APL2-CP-PNH-204	C5 inhibitor-naïve adult subjects with PNH	Open-label, multi-ascending dose study	Cohort 2: Pegcetacoplan 270 mg/day SC or 360 mg/day	Up to 1 year	To assess the safety, tolerability, preliminary efficacy and PK of multiple SC doses of pegcetacoplan in subjects with PNH who have no received treatment with eculizumab in the past	20 subjects	Completed

Trial Identifier	Trial Population	Trial Design	Treatment Dosing	Treatment Duration	Primary Objectives	Sample Size	Status
CP0514	C5 inhibitor-experienced subjects with PNH	Phase 1b open-label, single and multi-ascending dose study	Cohort 4: Pegcetacoplan 270 to 440 mg/d add-on therapy for up to 2 years Pegcetacoplan monotherapy transition from Day 252 to Day 626: 270 to 440 mg/day	Approximately 815 days	To assess the safety, tolerability, and PK of single and multiple SC doses of pegcetacoplan in subjects with PNH who are still anemic during treatment with eculizumab	6 subjects	Completed
APL2-307	Subjects with PNH previously treated with pegcetacoplan	Phase 3, open-label, nonrandomized, extension study	Pegcetacoplan 1,080 mg twice weekly or pegcetacoplan 1,080 mg every 3 days	4 years or until the development program for pegcetacoplan in subjects with PNH is terminated	To evaluate the long-term safety and efficacy of pegcetacoplan in the treatment of PNH (extension)	Planned: 160 subjects	Ongoing
APL2-308	C5 inhibitor-naïve subjects with PNH	Phase 3, randomized, open-label controlled study	Pegcetacoplan 1,080 mg twice weekly or pegcetacoplan 1,080 mg every 3 days Standard of care control (no pegcetacoplan)	Approximately 38 weeks	To evaluate the efficacy, safety, and tolerability of pegcetacoplan in subjects with PNH	Planned: 54 subjects	Ongoing

Source: Clinical reviewer.
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for Phase 1 and pharmacokinetic studies.
Abbreviations: C, complement protein; Hb, hemoglobin; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria; RCP, randomized control period; SC, subcutaneous

4. Patient Experience Data

In the Phase 3 trial, Study APL2-302, patient-reported outcomes were assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score (Table 4). Noninferiority was not assessed for FACIT-F score because of the break in the prespecified hierarchical testing order, but mean scores increased by 9 points in the pegcetacoplan group at Week 16. The adjusted least squares mean (LSM) change from baseline (CFB) in FACIT-F score at Week 16 was 9.22 versus -2.64 points, respectively. In addition, more subjects in the pegcetacoplan group achieved an improvement of >3 points in the FACIT-F score (73.2% versus 0% in the eculizumab group). However, no claims for patient-reported outcomes can be made because noninferiority could not be assessed due to a break in hierarchical testing.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	Section 6
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Pegcetacoplan is a complement inhibitor
Mechanism of action	Pegcetacoplan binds to complement protein (C) 3 and its activation fragment C3b, thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation. In PNH, extravascular hemolysis (EVH) is facilitated by C3b opsonization whereas intravascular hemolysis (IVH) is mediated by the downstream membrane attack complex (MAC). Pegcetacoplan acts proximally in the complement cascade controlling both C3b-mediated EVH and terminal complement-mediated IVH.
Active moieties	Two 15-amino-acid peptides (chemically bound to each end of linear polyethylene glycol [PEG])
QT prolongation	At the recommended dose of pegcetacoplan, no large mean increase (i.e., >20 ms) in QTc interval is observed.
	General Information
Bioanalysis	Pegcetacoplan concentrations in serum were measured using validated LC-MS/MS methods.
Healthy subjects versus patients	Patients with PNH are predicted to have lower pegcetacoplan exposures than healthy subjects because of increased systemic clearance. The effective half-life of pegcetacoplan at an SC dose of 1,080 mg twice weekly is estimated as 8.0 days for patients with PNH compared to 10.1 days for healthy subjects.
Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)	In Study APL2-302, 1,080 mg pegcetacoplan was given twice weekly and pegcetacoplan concentrations were measured weekly (or every 2 weeks) during the 4-week run-in period and the following 16-week randomized control period (RCP). Serum pegcetacoplan concentrations reach steady state approximately 4 to 6 weeks after the first dose. During the RCP, mean (%CV) serum steady-state trough concentrations of pegcetacoplan ranged between 655 (18.6%) µg/mL at Week 2 and 706 (15.1%) µg/mL at Week 16 in patients with PNH.
Range of effective dosage(s) or exposure	Based on the exposure-response analysis, steady-state trough concentrations of pegcetacoplan at 272 µg/mL, 396 µg/mL, and 597 µg/mL are predicted to be associated with 50%, 90%, and 99% of the maximum Hb response.
Maximally tolerated dosage or exposure	The maximum studied pegcetacoplan dose is a single SC dose of 2600 mg. No major safety issue was identified at this dose.
Dosage proportionality	Exposure of pegcetacoplan increases proportionally over a dose range of 45 to 1440 mg.
Accumulation	Upon 1,080 mg twice-weekly dosing, accumulation ratio is about 2.6-fold based on trough concentrations following the first dose and under steady-state conditions.
Time to achieve steady-state	Steady-state serum concentrations following twice weekly dosing at 1,080 mg in patients with PNH are achieved approximately 4 to 6 weeks following the first dose.

Characteristic	Drug Information
	Pharmacologic Activity
Bridge between to-be-marketed and clinical trial formulations	Not applicable (N/A), pegcetacoplan drug product used in the pivotal Phase 3 clinical study was the same dosage form and composition as the intended to-be-marketed product
	Absorption
Bioavailability	The bioavailability of pegcetacoplan following SC administration is approximately 87%
T_{max}	Geometric mean T_{max} ranges between 4.5 to 6 days
Food effect (fed/fasted) Geometric least squares mean and 90% CI	N/A—pegcetacoplan is administered via SC infusion
	Distribution
Volume of distribution	The mean (%CV) volume of distribution of pegcetacoplan is approximately 3.9 L (35%) in patients with PNH
Plasma protein binding	N/A
Drug as substrate of transporters	Pegcetacoplan is not a substrate of the transporters OAT1, OAT3, OCT2, OATP1B1, OATP1B3, P-gp, or BCRP
	Elimination
Mass balance results	Not available
Clearance	The estimated mean (CV%) of clearance is 0.37 L/day (28%)
Half-life	Median effective half-life of elimination ($t_{1/2}$) is 8.0 Days in patients with PNH
Metabolic pathway(s)	Metabolized by degradation into small peptides and individual amino acids
Primary excretion pathways (% dosage)	Catabolism in plasma
	Intrinsic Factors and Specific Populations
Body weight	Body weight is a PK covariate of pegcetacoplan. However, body weight is not expected to have a clinically meaningful impact on the Hb response and thus does not warrant a dose adjustment.
Age	There are no clinically significant differences in the PK of pegcetacoplan based on age (19 to 81 years old)
Renal impairment	Renal impairment with CrCl <30 mL/min had no significant impact on the PK of pegcetacoplan in comparison to healthy controls
Hepatic impairment	There are no clinically significant differences in the PK of pegcetacoplan based on hepatic function as evaluated by total bilirubin (0.3-4.3 mg/dL), albumin (3.6-4.9 g/dL), aspartate aminotransferase (13-116 IU/L), or alanine aminotransferase (9-59 IU/L)
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	In vitro studies showed that pegcetacoplan had no inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 and no induction of CYP1A1, CYP2B6, or CYP3A4
Inhibition/induction of transporter systems	In vitro studies showed that pegcetacoplan was not an inhibitor of the transporters OAT1, OAT3, OCT2, OATP1B1, OATP1B3, P-gp, or BCRP

Characteristic	Drug Information
Pharmacologic Activity	
Immunogenicity	
Bioanalysis	The assays to evaluate antipegcetacoplan peptide antibodies and their neutralizing ability may be subject to interference by on-board pegcetacoplan and are not adequate to determine the true incidence of antibodies and their clinical impact. Assay to determine anti-EPG antibodies is adequate (see Section III.14.4).
Incidence	In Study APL2-302, 2 of 80 patients with PNH (both in eculizumab group) were confirmed to have anti-pegcetacoplan antibodies at Week 16. However, due to the ADA assay deficiency, the incidence of antibody formation may be underestimated. Two other patients developed treatment-emergent or treatment-boosted anti-PEG antibodies (one occurrence for each case).
Clinical impact	For the two subjects with positive anti-pegcetacoplan antibodies in Study APL2-302, no significant impact on PK, safety, or Hb response was observed. However, both patients received only 4 weeks of pegcetacoplan treatment, and the sample size is too small to conclude the potential clinical impact of anti-pegcetacoplan antibodies. No clinically significant differences in the PK/PD, efficacy, or safety profile of pegcetacoplan were observed in patients who tested positive for anti-PEG antibodies.

Source: Reviewer's table based on data from Sections of Intrinsic Factors, Drug Interaction and Clinical Pharmacology Appendix.
Abbreviations: ADA, antidrug antibody; BCRP, breast cancer resistance protein; C, complement protein; CI, confidence interval; CrCl, creatinine clearance; CV, coefficient of variation; CYP, cytochrome P450; ELISA, enzyme-linked immunosorbent assay; EPC, established pharmacologic class; EVH, extravascular hemolysis, Hb, hemoglobin; IVH, intravascular hemolysis; LC-MS/MS, liquid chromatography with tandem mass spectrometry; MAC, membrane attack complex; OAT, organic anion transporter; OCT, organic cation transporter; PD, pharmacodynamics; PEG, polyethylene glycol; P-gp, P-glycoprotein; PK, pharmacokinetics; PNH, paroxysmal nocturnal hemoglobinuria; QT, QT interval; QTc, corrected QT interval; RCP, randomized control period; SC, subcutaneous; $t_{1/2}$, half-life of elimination, T_{max}, time to maximum concentration

5.1. Nonclinical Assessment of Potential Effectiveness

5.1.1. Primary Pharmacology

Pegcetacoplan at nanomolar concentrations binds to C3 with a binding constant of 15.6nM (Table 6). Stoichiometrically, one molecule of pegcetacoplan may bind with two C3 molecules, one for each peptide domain. It should be noted that pegcetacoplan binds to both C3 and C3b.

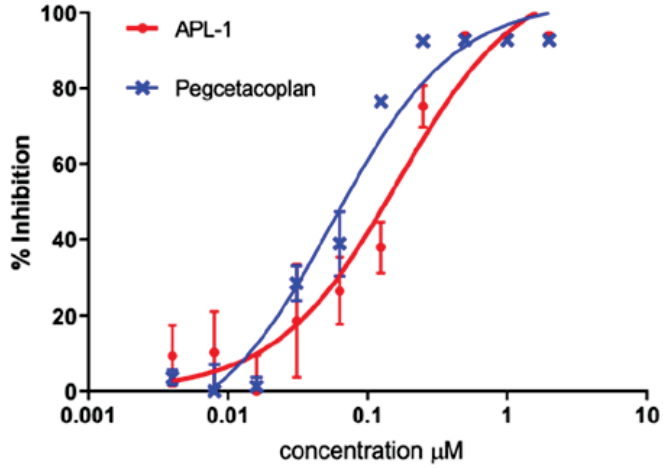
Table 6. Pegcetacoplan Binding and Stoichiometry to C3 and C3b

Ligand	C3 K_d, nM	C3, N	C3b K_d, nM	C3b, N
Pegcetacoplan	15.6	0.517	21.3	0.518

Source: Study Report 1XTPH-001, Table 1.
Abbreviations: K_d, binding constant; N, binding stoichiometry

The complement inhibitory activity of pegcetacoplan was investigated against both the classical and alternative activation pathways (Figure 2). The inhibitory activities of pegcetacoplan against the classical and alternative pathways were similar (half-maximal effective concentration [EC_{50}] 136nM versus 64nM). When the inhibitory effect of pegcetacoplan was compared to a non-PEGylated version of the peptide (APL-1), PEGylation was found to shift the inhibitory dose-response curve minimally to the left (pegcetacoplan EC_{50} 57nM versus APL-1 EC_{50} 165nM).

Figure 2. Human Alternative Pathway Inhibition Assay

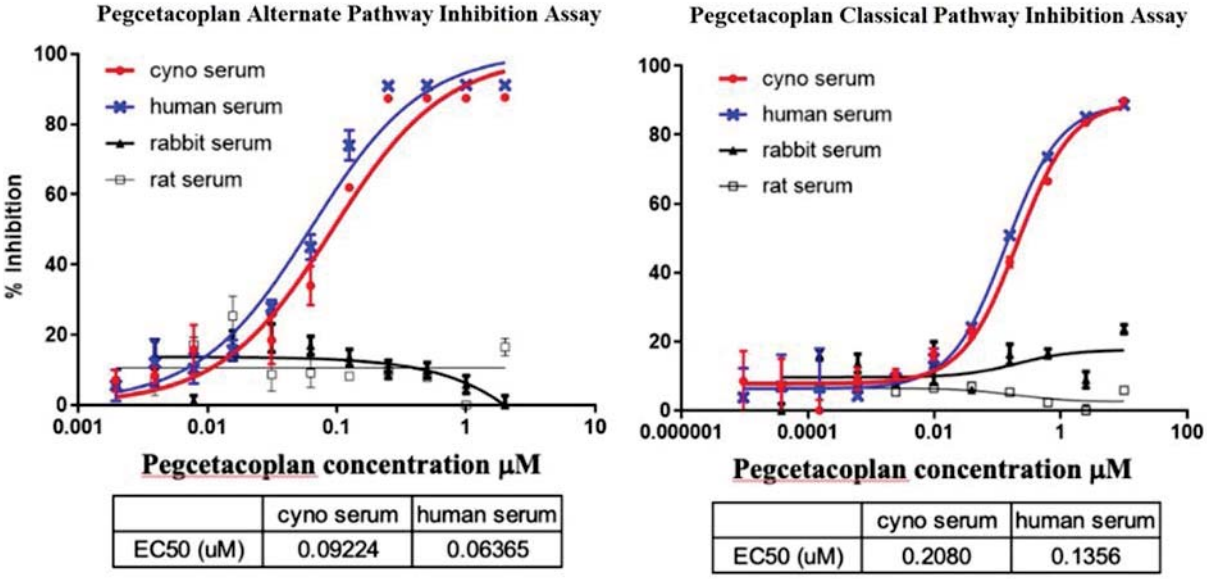


	APL-1	Pegcetacoplan
EC50 (uM)	0.1648	0.05695

Source: Study report 19CFPH-001, Apellis Pharmacology Summary Figure 3.
Abbreviations: APL-1, non-PEGylated version of pegcetacoplan; EC_{50}, half-maximal effective concentration

Pegcetacoplan is equally effective in inhibiting human and cynomolgus monkey plasma complement but has no or minimal activity in mice, rats, rabbits, and pigs. Therefore, the monkey served as the principal animal model for the nonclinical program (Figure 3).

Figure 3. Pegcetacoplan Alternate and Classical Pathway Inhibition Assays



	cyno serum	human serum
EC50 (uM)	0.09224	0.06365

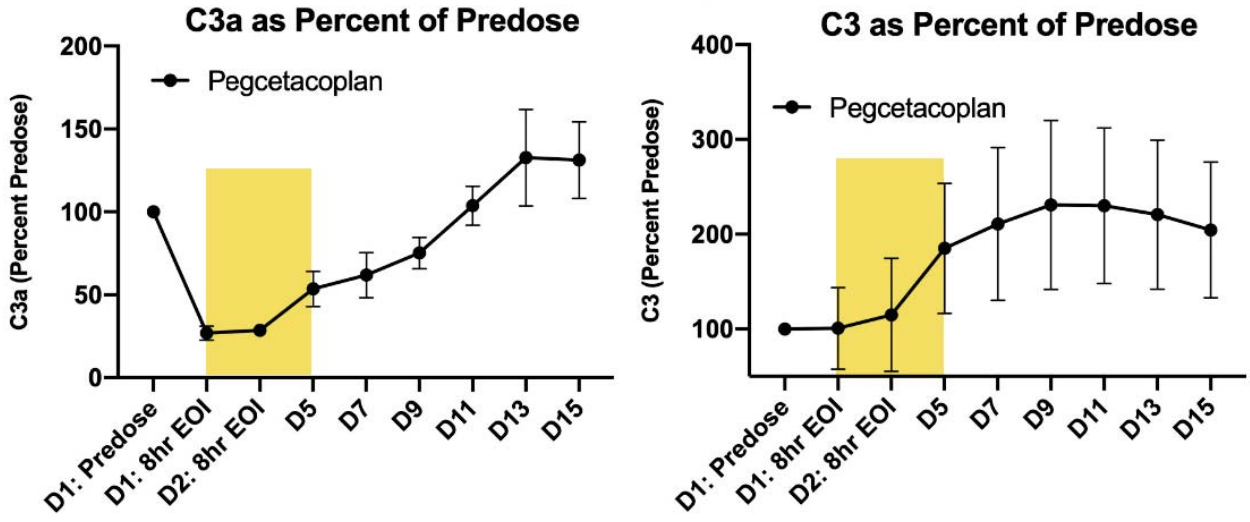
	cyno serum	human serum
EC50 (uM)	0.2080	0.1356

Source: Study Report 19CFPH-001, Apellis Pharmacology Summary Figure 4.
Abbreviation: cyno, cynomolgus; EC_{50}, half-maximal effective concentration

5.1.2. Animal Model Data Showing Proof of Concept

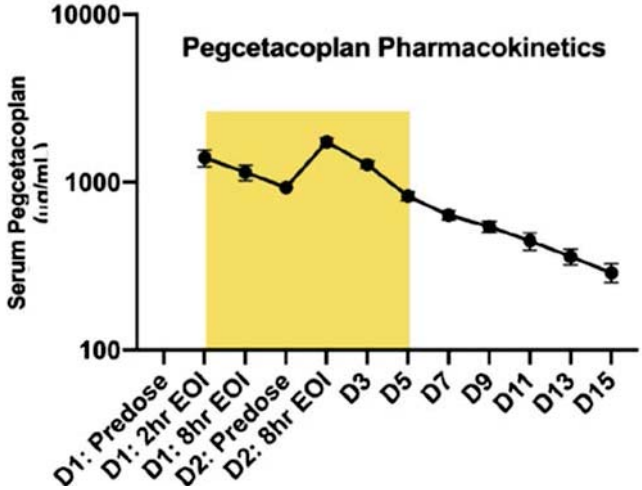
IV infusion of pegcetacoplan (84 mg/kg) to monkeys inhibited C3 processing as measured by an increase in C3 level and a decrease in C3a level in blood (Figure 4). This inhibitory action on C3 processing lasted for at least 5 Days and corresponded to an elevated plasma pegcetacoplan level (Figure 5); the prolonged activity likely reflects the effect of PEGylation on lengthening exposure to pegcetacoplan. No in vivo study was conducted in rodents because of the lack of drug pharmacology information.

Figure 4. Effect of Pegcetacoplan on C3 Processing



Source: Study 20095352, Apellis Pharmacology Summary, Figure 5.
Abbreviations: C3a, Complement 3a; D, day; EOI, end of infusion; hr, hour

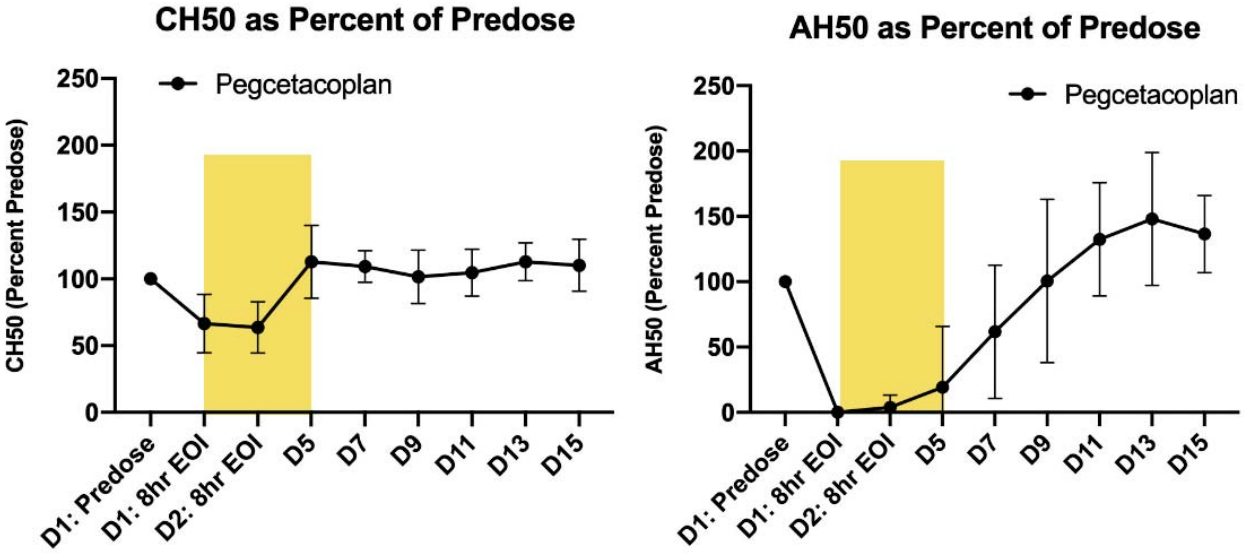
Figure 5. Serum Concentration of Pegcetacoplan Following Two Daily 60 Min IV Infusions in Cynomolgus Monkeys



Source: Study 20095352, Apellis Pharmacology Summary, Figure 5.
Abbreviations: D, day; EOI, end of infusion; hr, hour; IV, intravenous

Pegcetacoplan consistently decreased alternative C hemolytic activity and to a lesser degree total hemolytic C activity, perhaps indicating a greater impact on the alternative pathway. Antihemolytic activity persisted for at least 5 Days postdose in monkeys and was correlated with the pegcetacoplan serum concentration (Figure 6).

Figure 6. Effect of Pegcetacoplan on Complement Activation and C3 Breakdown in Cynomolgus Monkeys Following Two Daily 60 Min IV Infusions



Source: Study 20095352, Apellis Pharmacology Summary, Figure 6.
Abbreviations: AH50, alternative C hemolytic activity; CH50, hemolytic C activity; D, day; EOI, end of infusion; hr, hour; IV, intravenous

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

6.1.1. APL2-302

The Applicant's proposed dose is 1,080 mg BIW via SC infusion. The dose can be increased to 1,080 mg every 3 Days if a subject has an LDH level greater than two-fold the upper limit of normal. In the pivotal Phase 3 study (Study APL2-302), 41 patients with PNH received pegcetacoplan treatment at the proposed dose of 1,080 mg BIW during the randomized control period (RCP), with 2 patients requiring a dose increase to 1,080 mg every 3 days. The proposed dosing regimen is acceptable for approval based on the favorable efficacy and safety and the pharmacokinetic/pharmacodynamic (PK/PD) results from Study APL2-302, the population PK analysis, and the exposure-response (E-R) analysis in patients with PNH.

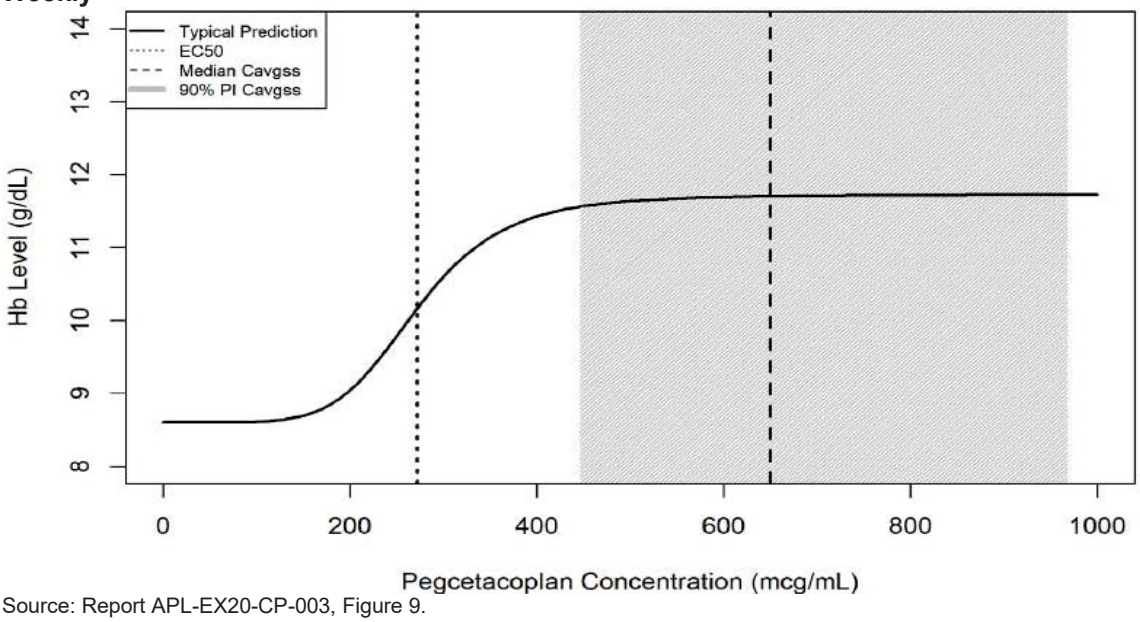
Dose Selection

Dose selection for Study APL2-302 was guided based on PK, efficacy, and safety data from three Phase 1 or Phase 2 trials (Studies APL2-202, APL2-204, and CP0514) in 30 patients with PNH. The cumulative data from these studies showed that hematologic responses increased in a dose-dependent manner with clinically meaningful Hb responses at doses of 270 mg/day to 360 mg/day. To reduce the burden of daily dosing and to promote dosing compliance, less-frequent dosing regimens were considered. The dosing regimen of 1,080 mg BIW (309 mg/day) or every 3 Days (360 mg/day) were selected based on the projected comparable pegcetacoplan exposures to those with 270 and 360 mg daily regimens, which were later confirmed in Study APL2-101 prior to the initiation of Study APL2-302.

Exposure-Response Analysis of Hb Level

The Applicant's E-R analyses suggest a concentration-dependent Hb response in patients with PNH. The E-R relationship between pegcetacoplan concentrations and Hb levels is described by a sigmoidal model of estimated maximal proportional CFB (E_{max}). The estimated E_{max} of Hb was a 36.3% increase from baseline. The EC_{50} of pegcetacoplan was 272 µg/mL. At the proposed dose (1,080 mg BIW SC), the expected average concentration at steady state of 650 µg/mL is expected to achieve a near-maximal effect on Hb response (Figure 7). Individuals with higher baseline Hb values and lower creatinine clearance (CrCl) are predicted to have a lesser response, in terms of Hb E_{max}. Eculizumab treatment status at baseline is not expected to have a meaningful effect on the Hb response.

Figure 7. Typical Predicted Hb Level and Response Following Pegcetacoplan 1,080 mg SC Twice Weekly



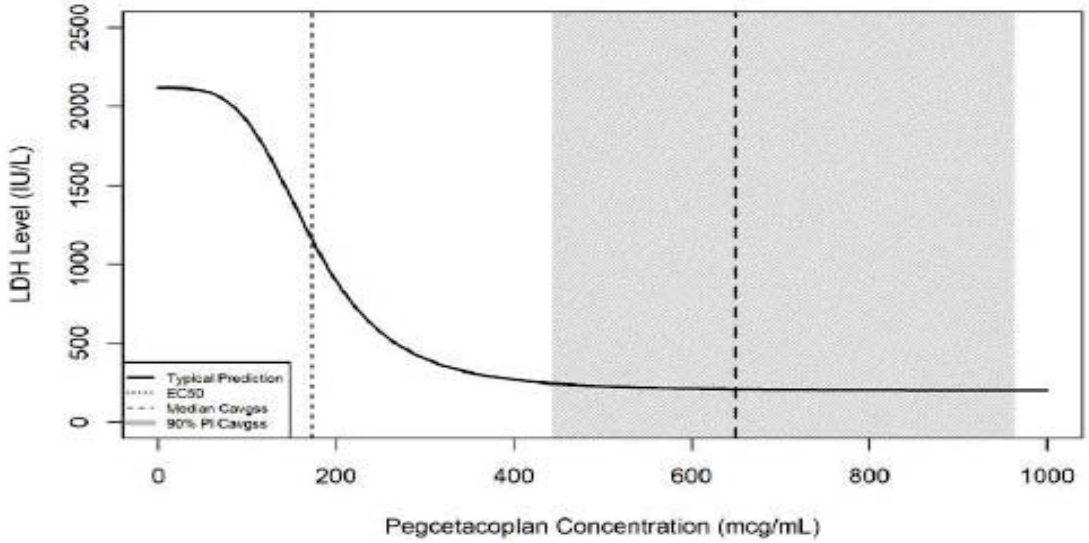
Source: Report APL-EX20-CP-003, Figure 9.
Abbreviations: $C_{avg,ss}$, average concentration at steady state; EC_{50}, half-maximal effective concentration; Hb, hemoglobin; PI, prediction interval; SC subcutaneous

Exposure-Response Analysis of LDH Level

The E-R relationship for LDH response was described using a sigmoidal E_{max} model. The E-R relationships differed between patients with/without eculizumab treatment at baseline. For patients without eculizumab treatment at baseline, E_{max} was a 90.8% decrease from baseline with an EC_{50} of 173 µg/mL Figure 8). For patients on eculizumab treatment at baseline, E_{max} was a 32.5% decrease from a baseline with an EC_{50} of 250 µg/mL Figure 9). The different E-R relationships are mainly driven by the different baseline LDH levels between the two patient groups. The eculizumab-naïve patients had an almost 8.5-fold higher LDH level at baseline (2117 IU/L) compared to that in eculizumab-treated patients (248 IU/L).

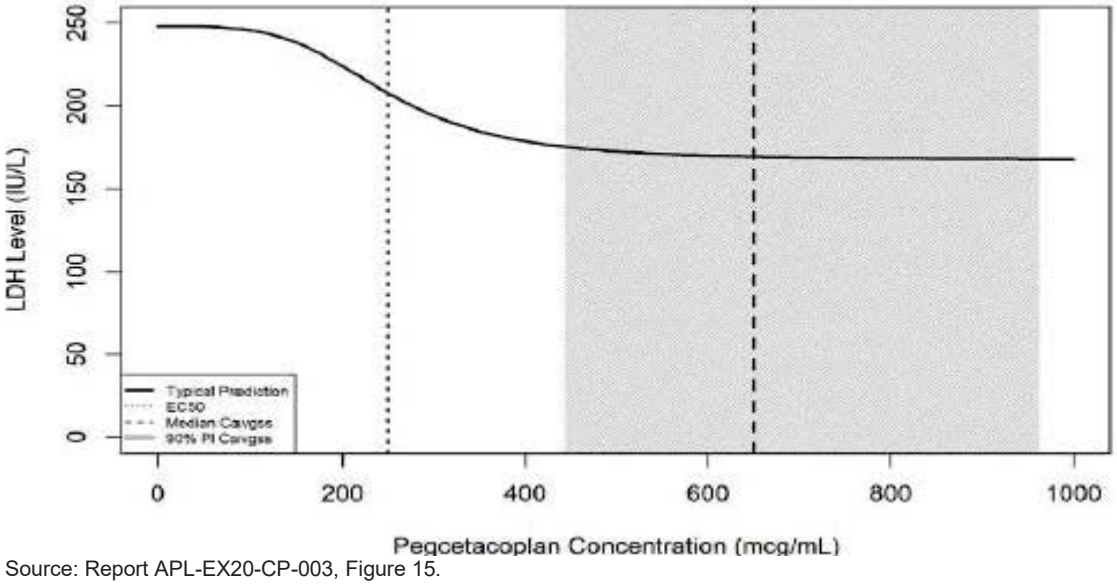
Although the magnitudes of E_{max} were different depending on eculizumab status at baseline, the EC_{50} estimates were similar. At the proposed dose, the pegcetacoplan exposures are expected to achieve close to the maximal effect for LDH control for both eculizumab-naïve and eculizumab-experienced patients with PNH.

Figure 8. Typical Predicted LDH Response and Level Following Pegcetacoplan 1,080 mg SC Twice Weekly in Eculizumab-Naïve Patients



Source: Report APL-EX20-CP-003, Figure 15.
Abbreviations: $C_{avg,ss}$, average concentration at steady state; EC_{50}, half-maximal effective concentration; Hb, hemoglobin; LDH, lactate dehydrogenase; PI, prediction interval; SC subcutaneous

Figure 9. Typical Predicted LDH Response and Level Following Pegcetacoplan 1,080 mg SC Twice Weekly in Patients Being Treated With Eculizumab



Source: Report APL-EX20-CP-003, Figure 15.
Abbreviations: $C_{avg,ss}$, average concentration at steady state; EC_{50}, half-maximal effective concentration; Hb, hemoglobin; LDH, lactate dehydrogenase; PI, prediction interval; SC subcutaneous

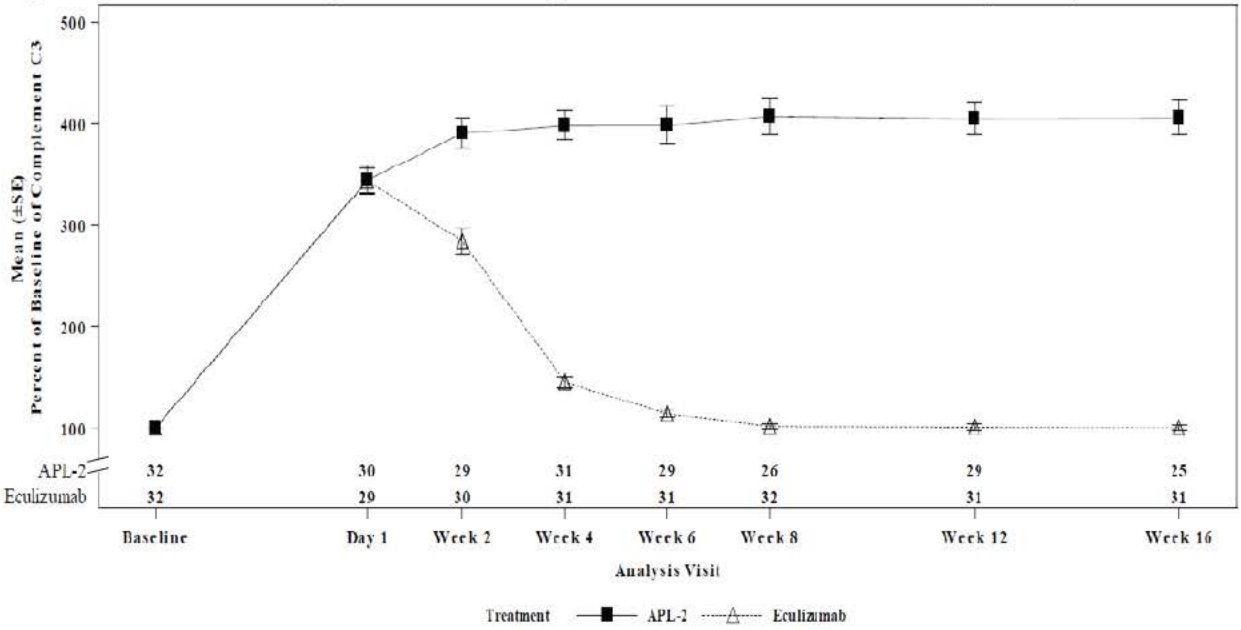
PD Biomarkers Supporting the Effectiveness of Pegcetacoplan

The effects of pegcetacoplan on complement PD biomarkers provide supportive evidence for the effectiveness of pegcetacoplan for PNH treatment. Based on the mechanism of action, pegcetacoplan is expected to protect PNH RBCs from complement-mediated destruction by inhibiting C3 activation, leading to decreased C3 deposition on PNH RBCs, and an increased proportion of PNH RBC clones that do not express CD59 (Type III cells) or express a low level of CD59 (Type II cells).

In Study APL2-302, PD biomarkers were measured at baseline (beginning of the run-in period) and every week throughout the 16-week RCP. The mean total C3 concentration increased from 0.94 g/L at baseline to 3.83 g/L at Week 16 in patients with PNH administered multiple doses of pegcetacoplan (Figure 10). The baseline percentage of PNH Type II and III RBCs was 66.8%, which increased to 93.9% at Week 16 (Figure 11). The mean percentage of PNH Type II and III RBCs with C3 deposition was 17.7% at baseline and decreased to 0.20% at Week 16 (Figure 12). In contrast, the levels of these three PD biomarkers were comparable between baseline and Week 16 for the eculizumab group.

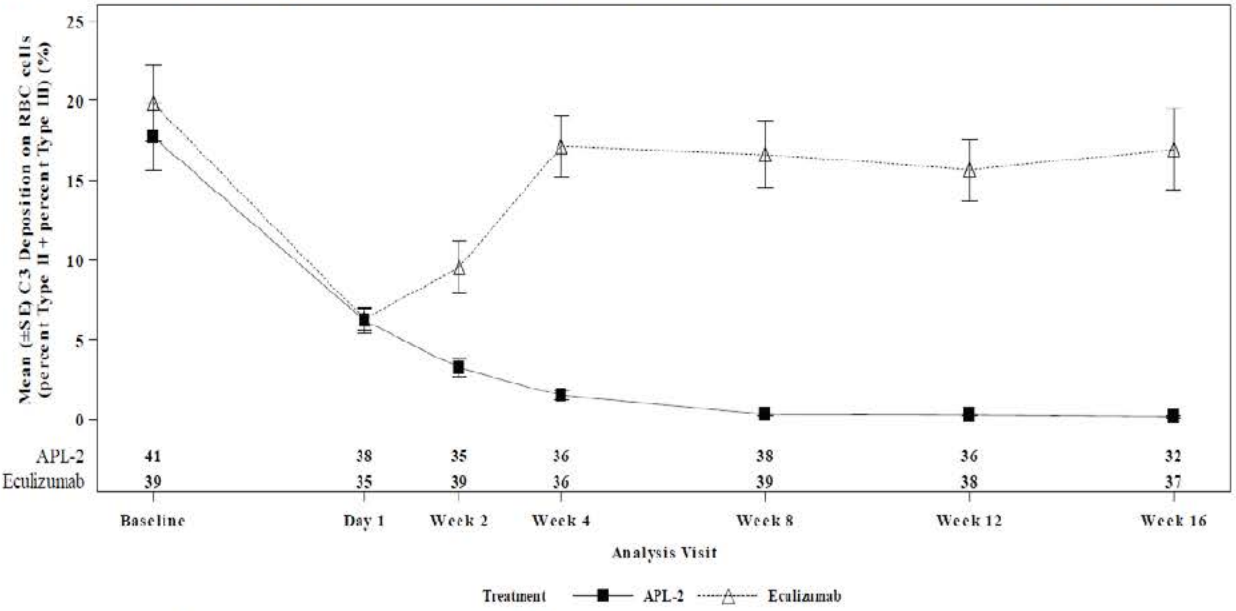
In summary, the observed changes in PD biomarkers—serum C3 level, proportion of PNH Type II and III RBCs, and C3 deposition on those RBCs—support its mechanism of action and provide mechanistic evidence for pegcetacoplan as an effective treatment for PNH.

Figure 10. Mean Percentage C3 Level During the Randomized Control Period (PD Set)



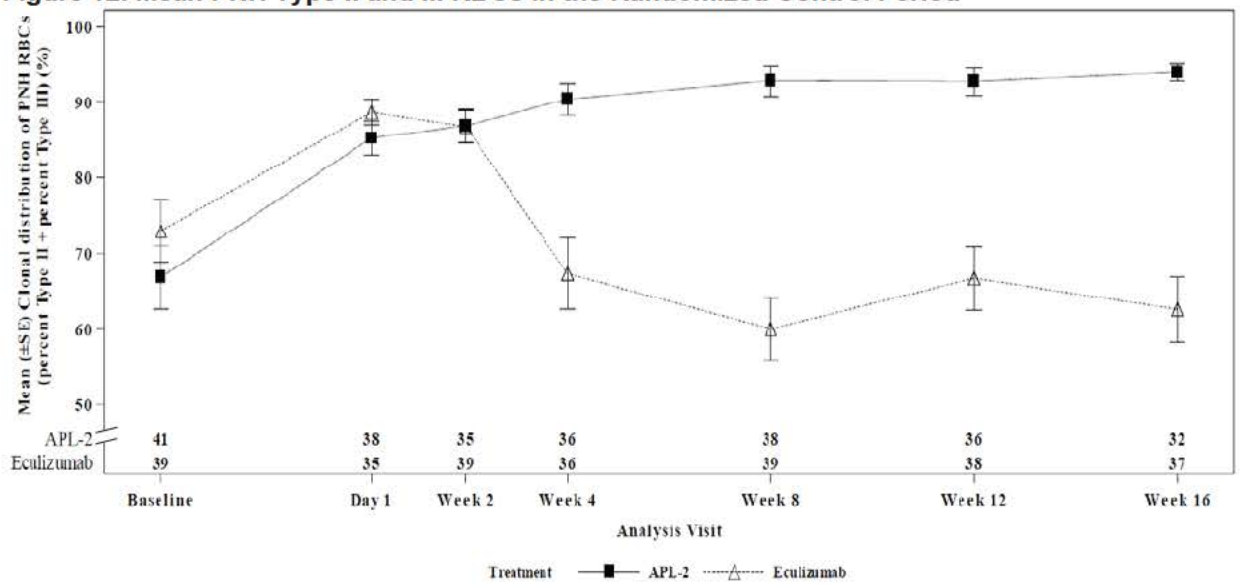
Source: Study APL2-302 Clinical Study Report, Figure 14.3.7.3.
Vertical bars represent standard errors.
Abbreviations: APL-2, pegcetacoplan; C, complement protein; PD, pharmacodynamics; SE, standard error

Figure 11. Mean PNH Type II and III RBCs Opsonized With C3 in the Randomized Control Period



Source: Study APL2-302 Clinical Study Report Figure 14.3.7.1.
Vertical bars represent standard errors.
Abbreviations: APL-2, pegcetacoplan; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; SE, standard error

Figure 12. Mean PNH Type II and III RBCs in the Randomized Control Period



Source: Study APL2-302 Clinical Study Report Figure 14.3.7.2.
Vertical bars represent standard errors.
Abbreviations: APL-2, pegcetacoplan; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; SE, standard error

6.2. Clinical Studies Intended to Demonstrate Efficacy

In support of the proposed indication, the Applicant conducted a single Phase 3 trial entitled, *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)*. The trial (APL2-302) was conducted from June 14, 2018, to November 14, 2019, at 44 sites in 11 countries (18% of the enrolled patients were in the United States). Study APL2-302 intends to support a claim of efficacy for the product in the proposed indication through the superior CFB in Hb level at Week 16 for the product compared to the control.

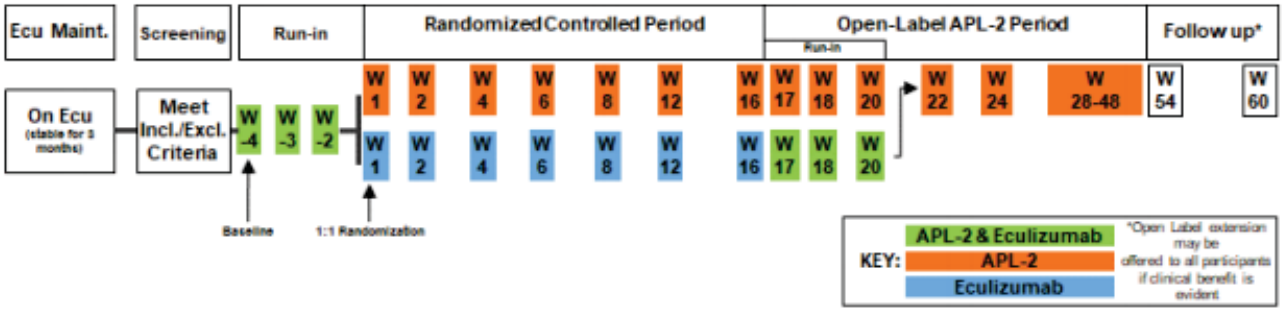
6.2.1. Study APL2-302

6.2.1.1. Design, APL2-302

Study APL2-302 was a prospective, Phase 3, randomized, multicenter, open-label, active-comparator-controlled trial comparing pegcetacoplan to eculizumab in patients with PNH who continued to have Hb levels <10.5 g/dL despite treatment with eculizumab.

The treatment period consisted of three parts (Figure 13): A 4-week run-in period, a 16-week RCP, and a 32-week open-label pegcetacoplan period (patients who received eculizumab during the 16-week RCP continued to receive eculizumab for the first 4 weeks in addition to pegcetacoplan).

Figure 13. Study APL2-302 Design



Source: Study APL2-302 Clinical Study Report, Figure 1 (p. 42).
Abbreviations: APL-2, pegcetacoplan; Ecu, eculizumab; Excl, exclusion; Incl, inclusion; Maint, maintenance; W, week

6.2.1.2. Objectives, APL2-302

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

6.2.1.3. Endpoints, APL2-302

The primary efficacy endpoint was CFB to Week 16 in Hb level, excluding data before the RCP.

Key secondary efficacy endpoints were as follows:

- Transfusion avoidance, defined as the proportion of subjects who did not require a transfusion 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 LDH level.
- CFB to Week 16, excluding data before the RCP, in FACIT-F scale score, version 4.

6.2.1.4. Eligibility Criteria, APL2-302

Key inclusion criteria:

- At least 18 years of age.
- 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 at the screening visit.
- Platelet count >50,000/mm^3 at the screening visit.
- Absolute neutrophil count >500/mm^3 at the screening visit.

6.2.1.5. Data Sources, APL2-302

The clinical study report, protocol, statistical analysis plan, Statistical Analysis System transport datasets, Statistical Analysis System programs, and dataset reviewer's guides for the study were submitted electronically. The network path for the submissions is \\CDSESUB1\evsprod\NDA215014\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pnh\5351-stud-rep-contr\apl2-302. The network path for the analysis datasets is \\CDSESUB1\evsprod\NDA215014\0001\m5\datasets\apl2-302.

All submitted analysis datasets and tabulation datasets are in standardized format. The Applicant provided Statistical Analysis System programs for deriving safety and efficacy analysis datasets and for analysis of the efficacy endpoints.

6.2.1.6. Data Quality, APL2-302

In general, the data submitted by the Applicant to support the efficacy and safety of pegcetacoplan for the proposed indication are acceptable. No issues were discovered with respect to data quality or data integrity.

6.2.1.7. Statistical Analysis Plan, APL2-302

The primary analysis population of Study APL2-302 was the intent-to-treat (ITT) population, which consisted of all randomized patients. The safety population consisted of all randomized patients who received at least one dose of monotherapy study drug.

Analysis of the Primary Endpoint

The primary efficacy endpoint, the CFB in Hb level at Week 16 of the RCP, was analyzed using a mixed model for repeated measures as the primary analysis. The model included categorical effects of treatment, visit, stratification factors (transfusion history and platelet count at screening) and treatment-by-visit interaction, and a continuous covariate of baseline Hb level. An unstructured covariance structure was used to model the within-patient errors, and the Kenward–Roger approximation was used to estimate the denominator degrees of freedom. The treatment comparison for the primary endpoint was the difference between treatment groups at Week 16. LSMs for each treatment group, the difference in LSMs, a 95% confidence interval (CI) for the difference in LSMs, and the corresponding p-value were reported by the Applicant and are included in this review.

Analyses of Key Secondary Endpoints

Analyses of the key secondary efficacy endpoints were based on noninferiority tests. For each key secondary endpoint included in the multiple testing procedure, noninferiority was concluded if the appropriate limit of the 95% CI for the comparison between treatment groups indicated that pegcetacoplan was not inferior to eculizumab according to the prespecified noninferiority margin (NIM).

The binary key secondary efficacy endpoint of transfusion avoidance was analyzed by Cochran–Mantel–Haenszel test stratified by transfusion history and platelet count at screening. The treatment difference in responder proportions and 95% CI for the difference in proportions were calculated using the stratified Miettinen–Nurminen method.

The continuous key secondary efficacy endpoints of CFB at Week 16 of the RCP in ARC, LDH level, and FACIT-F scale score were analyzed using a mixed model for repeated measures with similar factors and covariates used for the primary endpoint. For those endpoints, the relevant baseline covariate was utilized in the model.

Multiple Testing Approach

To preserve the overall type 1 error rate, the primary endpoint was to be tested first at a two-sided alpha level of 0.05. If the primary endpoint was not significant at a two-sided alpha level of 0.05, testing of subsequent endpoints was to cease. If statistical significance was reached for the primary endpoint, the key secondary endpoints were to be tested in a hierarchical manner. Once one hypothesis tested was not statistically significant, all subsequent hypotheses were not to be assessed and were to be considered not significant.

Key secondary endpoints were to be tested at a one-sided alpha level of 0.025 according to the following order and NIM criteria:

- Transfusion avoidance: Lower bound of the 95% CI for the difference between responder proportions is greater than the NIM of -20%.
- CFB to Week 16 in ARC: Upper bound of the 95% CI for the treatment difference is less than the NIM of 10.
- CFB to Week 16 in LDH level: Upper bound of the 95% CI for the treatment difference is less than the NIM of 20.
- CFB to Week 16 in FACIT-F score: Lower bound of the 95% CI for the treatment difference is greater than the NIM of -3.

If noninferiority was demonstrated for all key secondary endpoints, superiority of the following key secondary endpoints was to be tested at a two-sided alpha level of 0.05:

- Transfusion avoidance.
- CFB to Week 16 in ARC.
- CFB to Week 16 in FACIT-F score.

The NIMs for the key secondary endpoints were not agreed upon beforehand with the FDA. As stated in communications issued to the Applicant, because of the FDA's concerns regarding the trial's design and statistical analysis plan, including the lack of justification for the proposed NIMs, acceptability of the study data to support application approval was to be a review issue. However, because the results for the first two key secondary endpoints (transfusion avoidance and CFB to Week 16 in ARC) demonstrated superiority of pegcetacoplan compared to eculizumab (Table 13 and Table 14), the concern regarding justification of the NIM no longer applied for those endpoints.

Handling of Missing Data

In the analyses of the primary and continuous key secondary efficacy endpoints, if a patient received a transfusion during the RCP or withdrew from the trial, the endpoint parameter values up to the time of transfusion or withdrawal were used in the analysis model, and subsequent parameter values were assigned as missing. In the analysis of the binary transfusion avoidance key secondary endpoint, patients who did not have a transfusion but withdrew from the trial before Week 16 were considered as having had a transfusion. In the analyses of the primary and key secondary efficacy endpoints, if a patient discontinued study treatment, subsequent parameter values collected after treatment discontinuation were used in the endpoint analyses.

6.2.1.8. Results of Analyses, APL2-302

Study APL2-302 enrolled patients from 44 sites in the North America, Europe, and Asia-Pacific regions. The ITT population comprised 80 patients who were randomized in the trial. Trial population definitions are listed in Table 7.

Table 7. Population Definitions in Study APL2-302

Population	Definition
ITT	All randomized patients
Safety	All randomized patients who received at least one dose of monotherapy study drug
PP	All patients in the ITT population who did not violate any inclusion or exclusion criteria and/or deviate from the protocol in a way that could influence their efficacy assessment
Completers	All patients in the ITT population who completed the Week 16 efficacy assessment

Source: Study APL2-302 Clinical Study Report, Section 9.7.3 (p. 69).
Abbreviations: ITT, intent-to-treat; PP, per protocol

6.2.1.9. Baseline Demographics, APL2-302

Demographic characteristics of the ITT population are summarized by treatment group in Table 8. Most patients were female (61.3%), white (61.3%), and not Hispanic or Latino (76.3%). The mean age was 48.8 years, ranging from 19 to 81 years. The mean patient weight was 75.25 kg, ranging from 51.0 to 155.7 kg. The mean height was 168.4 cm, ranging from 148.0 to 200.0 cm. Demographic characteristics were generally similar between treatment groups.

Table 8. Baseline Demographic Characteristics, ITT Population, APL2-302

Characteristic	Pegcetacoplan 1,080 mg (N=41)	Eculizumab (N=39)
Sex, n (%)		
Male	14 (34.1)	17 (43.6)
Female	27 (65.9)	22 (56.4)
Age, years		
Mean (SD)	50.2 (16.29)	47.3 (15.81)
Median (min, max)	53.0 (19, 81)	47.0 (23, 78)
Age ranges in years, n (%)		
≥17 to <65	31 (75.6)	32 (82.1)
≥65 to <75	7 (17.1)	6 (15.4)
≥75	3 (7.3)	1 (2.6)
Race, n (%)		
White	24 (58.5)	25 (64.1)
Asian	5 (12.2)	7 (17.9)
Black/African American	2 (4.9)	0
Other	0	1 (2.6)
Not reported	10 (24.4)	6 (15.4)
Ethnicity, n (%)		
Hispanic	2 (4.9)	1 (2.6)
Non-Hispanic	29 (70.7)	32 (82.1)
Not reported	10 (24.4)	6 (15.4)
Country of participation, n (%)		
United States	7 (17.1)	7 (18.0)
France	10 (24.4)	6 (15.4)
Germany	7 (17.1)	4 (10.3)
United Kingdom	6 (14.6)	5 (12.8)
Japan	5 (12.2)	5 (12.8)
Canada	3 (7.3)	1 (2.6)
Australia	1 (2.4)	4 (10.3)
Belgium	1 (2.4)	3 (7.7)
Spain	1 (2.4)	1 (2.6)
South Korea	0	1 (2.6)
Russia	0	2 (5.1)

Characteristic	Pegcetacoplan 1,080 mg (N=41)	Eculizumab (N=39)
Weight, kg		
Mean (SD)	75.86 (18.77)	74.60 (16.62)
Median (min, max)	73.2 (53.2, 155.7)	71.6 (51.0, 111.6)
Height, cm		
Mean (SD)	167.72 (10.27)	169.06 (8.72)
Median (min, max)	167.0 (148.0, 200.0)	168.0 (153.1, 187.0)

Source: Study APL2-302 Clinical Study Report, Table 14 (p. 93) and Table 14.1.4.2 (p. 267); statistical reviewer's analysis.
Abbreviations: ITT, intent-to-treat; max, maximum; min, minimum; N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation

Baseline clinical characteristics of the ITT population are summarized by treatment group in Table 9. The most common eculizumab dosing level and regimen was 900 mg every 2 weeks (70% of patients). Baseline mean Hb levels were generally similar between groups, with an overall mean of 8.69 g/dL.

The median time since diagnosis of PNH to Day -28 was longer in the eculizumab group than in the pegcetacoplan group (9.67 years versus 6.00 years). Although mean baseline LDH levels were higher in in the eculizumab group than in the pegcetacoplan group (308.6 U/L versus 257.5 U/L), median baseline LDH levels were lower in in the eculizumab group than in the pegcetacoplan group (212.0 U/L versus 247.0 U/L).

For both baseline variables of time since PNH diagnosis and baseline LDH level, we noted that the eculizumab group has larger mean values than the pegcetacoplan group, and patients with values above the 75th percentile were enrolled in all three trial regions. The longest observed times elapsed since PNH diagnosis were in the eculizumab group (33 years for one patient in the United States and 38 years for one patient in Germany). The highest observed baseline LDH levels were in the eculizumab group (1598 U/L for one patient in Japan and 1079 U/L for one patient in Russia). The statistical reviewer produced histograms for time since PNH diagnosis and baseline LDH level for the two treatment groups, and they are displayed in Figure 33 and Figure 35, respectively, in Section 16. The two figures show that the two treatment groups have closely overlapping distributions, which are both skewed to the right with some outliers.

Therefore, when considering the aforementioned distributions of time since diagnosis of PNH to Day -28 and baseline LDH level, along with the small sample size of the trial, the two baseline variables do not appear likely to have impacted the results in an unbalanced fashion.

Table 9. Baseline Clinical Characteristics, ITT Population, APL2-302

Characteristic	Pegcetacoplan 1,080 mg (N=41)	Eculizumab (N=39)
Time since diagnosis of PNH (years) to Day -28		
Mean (SD)	8.74 (7.36)	11.68 (9.58)
25th percentile	3.34	4.00
Median	6.00	9.67
75th percentile	12.00	16.00
Min, max	1.0, 31.0	1.0, 38.0
Duration of treatment with eculizumab (days) prior to Day -28		
Mean (SD)	1868 (1568)	1746 (1327)
Current eculizumab dosing level and dosing regimen, n (%)		
Every 2 weeks IV 900 mg	26 (63.4)	30 (76.9)
IV 900 mg[1]	1 (2.4)	0
Every 2 weeks IV 1200 mg	12 (29.3)	9 (23.1)
Every 2 weeks IV 1500 mg	2 (4.9)	0
Number of transfusions in the last 12 months prior to Day -28, n (%)		
<4	20 (48.8)	16 (41.0)
≥4	21 (51.2)	23 (59.0)
Platelet count at screening, n (%)		
<100,000 (count/mm^3)	12 (29.3)	9 (23.1)
≥100,000 count/mm^3)	29 (70.7)	30 (76.9)
Hemoglobin level (g/dL)		
Mean (SD)	8.69 (1.08)	8.68 (0.89)
ARC (10^9 cells/L)		
Mean (SD)	217.52 (74.96)	216.15 (69.14)
LDH level (U/L)		
Mean (SD)	257.5 (97.7)	308.6 (284.8)
25th percentile	195.5	189.0
Median	247.0	212.0
75th percentile	286.0	250.5
Min, max	118.5, 584.0	122.0, 1598.0
Baseline percentage of PNH type II and III RBCs		
Mean (SD)	66.8 (26.5)	72.9 (25.8)
Patients with ≥1 thrombosis history, n %)	15 (36.6)	10 (25.6)
Patients with concomitant anticoagulation therapy, n (%)	15 (36.6)	14 (36.0)

Source: Study APL2-302 Clinical Study Report Table 15 (p. 95), Table 14.1.5.2 (p. 280).
[1] Dosed once every 11 days.
Abbreviations: ARC, absolute reticulocyte count; ITT, intent-to-treat; IV, intravenous; LDH, lactate dehydrogenase; max, maximum; min, minimum; N, number of patients in treatment group; n, number of patients with given characteristic; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; SD, standard deviation

6.2.1.10. Disposition, APL2-302

Of the 102 patients screened, 80 entered the run-in period, received at least one dose of study drug in the run-in period, and entered the RCP. Of the 80 patients randomized, 1 (1.3%) patient discontinued and 79 (98.7%) completed the trial. Three patients in the pegcetacoplan group discontinued study drug because of an adverse event (AE), one of whom discontinued the trial due to an AE. Patient disposition is listed in Table 10 and Table 11.

Table 10. Patient Screening and Randomization, APL2-302

Disposition	Value
Number of patients screened	102
Number of patients not randomized	22
Number of screening failures, n (%)	21 (20.6)
Number of patients who completed screening but did not enter subsequent study periods, n (%)	1 (1.0)
Number of patients in the run-in period	80
Number of patients randomized	80

Source: Study APL2-302 Clinical Study Report, Table 14.1.2.1 (p. 259) and Table 14.1.2.2 (p. 260).
One patient (patient 01002001) completed the screening period but did not enter any subsequent study periods. Therefore, the total number of patients with data beyond the screening period was 80.
Abbreviation: n, number of patients with specified disposition

Table 11. Patient Disposition, APL2-302

Disposition Category	Pegcetacoplan 1,080 mg N=41 n (%)	Eculizumab N=39 n (%)
Patients randomized	41 (100)	39 (100)
ITT population	41 (100)	39 (100)
PP population	36 (87.8)	35 (89.7)
Safety population	41 (100)	39 (100)
Completers population	37 (90.2)	38 (97.4)
Discontinued study drug	3 (7.3)	0
Adverse event	3 (7.3)	0
Discontinued trial	1 (2.4)	0
Adverse event	1 (2.4)	0

Source: Study APL2-302 Clinical Study Report, Table 12 (p. 90) and Table 13 (p. 92).
Abbreviations: ITT, intent-to-treat; N, number of patients; n, number of patients with specified disposition; PP, per-protocol

6.2.1.11. Protocol Deviations, APL2-302

In the ITT population, 59 patients (73.8%) had major protocol deviations. A similar percentage of these deviations occurred in both treatment groups (70.7% in the pegcetacoplan group and 76.9% in the eculizumab group). Most major protocol deviations were due to *study assessments/schedule noncompliance* (45 patients [56.3%]). The next most common protocol deviations were as follows in order of frequency: *informed consent* (13 patients [16.3%]), *enrollment & inclusion/exclusion* (six patients [7.5%]), and *prohibited concomitant medication* (five patients [6.3%]).

6.2.1.12. Analysis of Primary Endpoint, APL2-302

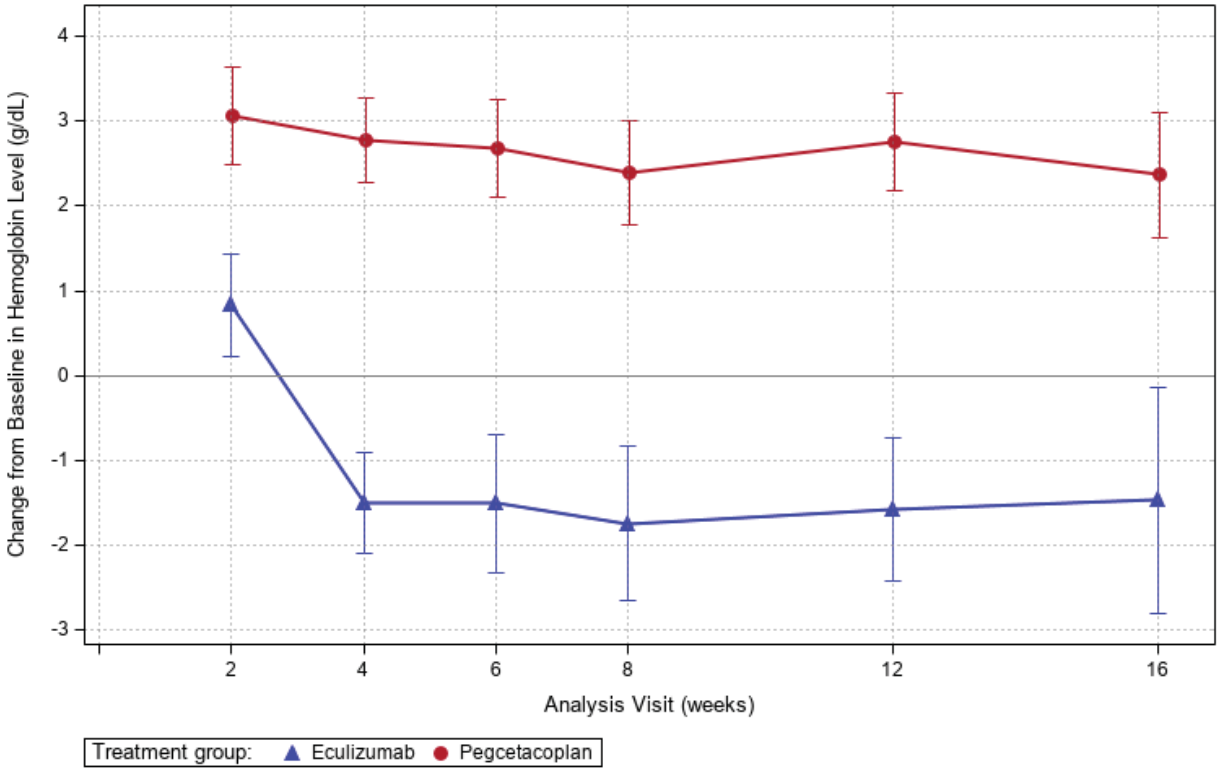
The primary efficacy endpoint was the CFB in Hb level at Week 16 of the RCP. The LSM CFB in Hb at Week 16 in the pegcetacoplan and eculizumab groups were 2.37 g/dL and -1.47 g/dL, respectively. The difference in LSMs between treatment groups was 3.84 g/dL, 95% CI (2.33 to 5.34), $p<0.0001$. These results are summarized for the ITT population in Table 12 and Figure 14.

Table 12. CFB in Hb Level at Week 16 of the RCP, ITT Population, APL2-302

Parameter	Value
LSM CFB in Hb (g/dL)[1] (95% CI)	
Pegcetacoplan 1,080 mg, N=41	2.37 (1.63, 3.10)
Eculizumab, N=39	-1.47 (-2.81, -0.13)
Difference in LSM between pegcetacoplan and eculizumab (95% CI)	3.84 (2.33, 5.34)
p-value for difference in LSM[2]	<0.0001

Source: Study APL2-302 Clinical Study Report, Table 21 (p. 104); statistical reviewer's analysis.
[1] Endpoint values after transfusion and study withdrawal were set to missing.
[2] P-value was based on a mixed model for repeated measures, which included the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.
Abbreviations: CFB, change from baseline; CI, confidence interval; Hb, hemoglobin; ITT, intent-to-treat; LSM, least squares mean; N, number of patients; RCP, randomized control period

Figure 14. Mean CFB in Hb Level During RCP by Visit and Treatment Group, ITT Population, APL2-302



Note: Treatment effect estimates from a mixed model are shown.
Note: The mixed model contained the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.
Note: Vertical lines represent 95% confidence intervals for least squares mean estimates.

Source: Statistical reviewer's analysis.
Endpoint values after transfusion and study withdrawal were set to missing.
Abbreviations: CFB, change from baseline; Hb, hemoglobin; ITT, intent-to-treat; RCP, randomized control period

A decrease in the serum hemoglobin level was noted in the eculizumab monotherapy arm between Weeks 2 to 4 during the 16-week treatment period of APL2-302 compared to the serum hemoglobin level in the pegcetacoplan arm. Although the evidence not conclusive, it is quite possible that the removal of pegcetacoplan at the start of the RCP results in unmasking of the extravascular hemolysis in the eculizumab arm, thereby leading to the decrease in serum

hemoglobin levels in patients receiving eculizumab monotherapy, as seen in Figure 14. This compares with the stable hemoglobin levels seen in Week 2 to Week 4 of the RCP in patients receiving pegcetacoplan monotherapy.

In the pegcetacoplan group, the LSM CFB values were similar from Week 2 to Week 16. In the eculizumab group, the LSM CFB values decreased from Week 2 to Week 4, and subsequently remained relatively constant to Week 16. Results by treatment week are shown in Table 76 in Section 16.

Sensitivity Analyses

The statistical reviewer conducted sensitivity analyses for the primary efficacy endpoint in the ITT population in order to examine the departures from the assumptions regarding missing data in the Applicant's prespecified efficacy analysis (Section 16). These sensitivity analyses demonstrated that the primary endpoint analysis results were robust to alternate scenarios for missing data assumptions.

6.2.1.13. Analysis of Secondary Endpoints, Study APL2-302

Key secondary endpoints for the RCP were as follows: the proportion of patients with transfusion avoidance; CFB in ARC at Week 16; CFB in LDH level at Week 16; and CFB in FACIT-F scale score at Week 16.

Transfusion Avoidance

At Week 16, 35 (85.4%) and 6 (15.4%) patients in the pegcetacoplan and eculizumab groups, respectively, did not require a transfusion (Table 13). The adjusted difference in proportions between treatment groups was 62.5% (95% CI 48.3 to 76.8, nominal p<0.0001). Because the lower bound of the 95% CI was greater than the prespecified NIM of -20%, noninferiority was met for this endpoint.

Table 13. Patients With Transfusion Avoidance During the RCP, ITT Population, APL2-302

Parameter	Value
Number (%) of patients with transfusion avoidance[1]	
Pegcetacoplan 1,080 mg, N=41	35 (85.4)
Eculizumab, N=39	6 (15.4)
Adjusted difference in proportions between pegcetacoplan and eculizumab (95% CI)[2]	62.5 (48.3, 76.8)
Nominal p-value for difference in proportions[3]	<0.0001

Source: Study APL2-302 Clinical Study Report, Table 28 (p. 114); statistical reviewer's analysis.
[1] Patients who did not have a transfusion but withdrew before Week 16 were considered as having a transfusion.
[2] Difference in proportions and 95% CI were based on the stratified Miettinen–Nurminen method.
[3] Nominal p-value was based on Cochran–Mantel–Haenszel chi-squared test stratified by transfusion history and platelet count at screening.
Abbreviations: CI, confidence interval; ITT, intent-to-treat; N, number of patients; RCP, randomized control period

CFB in ARC

The LSM CFB in ARC at Week 16 in the pegcetacoplan and eculizumab groups was -135.8×10^9 cells/L and 27.8×10^9 cells/L, respectively. The difference in LSMs between the treatment groups was -163.6×10^9 cells/L (95% CI -189.9 to -137.3, nominal p<0.0001) (Table 14). Because the upper bound of the 95% CI was less than the prespecified NIM of 10, noninferiority was met for this endpoint.

Table 14. CFB in ARC at Week 16 of the RCP, ITT Population, APL2-302

Parameter	Value
LSM CFB in ARC (×10^9 cells/L)[1] (95% CI)	
Pegcetacoplan 1,080 mg, N=41	-135.8 (-149.0, -122.6)
Eculizumab, N=39	27.8 (4.1, 51.5)
Difference in LSM between pegcetacoplan and eculizumab (95% CI)	-163.6 (-189.9, -137.3)
Nominal p-value for difference in LSM[2]	<0.0001

Source: Study APL2-302 Clinical Study Report, Table 29 (p. 115); statistical reviewer's analysis.
[1] Endpoint values after transfusion and study withdrawal were set to missing.
[2] Nominal p-value was based on a mixed model for repeated measures which included the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.
Abbreviations: ARC, absolute reticulocyte count; CFB, change from baseline; CI, confidence interval; ITT, intent-to-treat; LSM, least squares mean; N, number of patients; RCP, randomized control period

Results by treatment week are shown in Table 77 and Figure 34 in Section 16. In the pegcetacoplan group, the LSM CFB values remained relatively constant from Week 2 to Week 16. In the eculizumab group, the LSM CFB values increased from Week 2 to Week 4, and subsequently remained relatively constant to Week 16, except for a decrease at Week 12.

CFB in LDH Level

The LSM CFB in LDH level at Week 16 in the pegcetacoplan and eculizumab groups were -14.8 U/L and -10.1 U/L, respectively. The difference in LSMs between the treatment groups was -4.6 U/L (95% CI -181.3 to 172.0, nominal p=0.96) (Table 15). Because the upper bound of the 95% CI was not less than the prespecified NIM of 20, noninferiority was not met for this endpoint.

Table 15. CFB in LDH Level at Week 16 of the RCP, ITT Population, APL2-302

Parameter	Value
LSM CFB in LDH (U/L)[1] (95% CI)	
Pegcetacoplan 1,080 mg, N=41	-14.8 (-107.9, 78.4)
Eculizumab, N=39	-10.1 (-162.3, 142.0)
Difference in LSM between pegcetacoplan and eculizumab (95% CI)	-4.63 (-181.3, 172.0)
Nominal p-value for difference in LSM[2]	0.96

Source: Study APL2-302 Clinical Study Report, Table 31 (p. 118); statistical reviewer's analysis.
[1] Endpoint values after transfusion and study withdrawal were set to missing.
[2] Nominal p-value was based on a mixed model for repeated measures which included the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.
Abbreviations: CFB, change from baseline; CI, confidence interval; ITT, intent-to-treat; LDH, lactate dehydrogenase; LSM, least squares mean; N, number of patients; RCP, randomized control period

Results by treatment week are shown in Table 78 and Figure 36 in Section 16. By Week 8, the LSM CFB values were similar between the two treatment groups. In an exploratory analysis that excluded two patients with outlier baseline LDH levels, the conclusion regarding noninferiority for the endpoint did not change (Table 79 in Section 16).

CFB in FACIT-F Score

Because noninferiority was not met for the LDH endpoint, results for the FACIT-F score endpoint are considered exploratory (b) (4) The LSM CFB in FACIT-F scores at Week 16 in the pegcetacoplan and eculizumab groups was 9.2 and -2.6,

respectively. The difference in LSMs between the treatment groups was 11.9 (95% CI 5.5 to 18.3, nominal p=0.0005) (Table 15, Table 16). The lower bound of the 95% CI was greater than the prespecified NIM of -3.

Table 16. CFB in FACIT-F Score at Week 16 of RCP, ITT Population, APL2-302

Parameter	Value
LSM CFB in FACIT-F score[1] (95% CI)	
Pegcetacoplan 1,080 mg, N=41	9.22 (5.96, 12.48)
Eculizumab, N=39	-2.65 (-8.29, 2.99)
Difference in LSM between pegcetacoplan and eculizumab (95% CI)	11.87 (5.49, 18.25)
Nominal p-value for difference in LSM[2]	0.0005

Source: Study APL2-302 Clinical Study Report, Table 33 (p. 121); statistical reviewer's analysis.
[1] Endpoint values after transfusion and study withdrawal were set to missing.
[2] Nominal p-value was based on a mixed model for repeated measures which included the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.
Abbreviations: CFB, change from baseline; CI, confidence interval; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; ITT, intent-to-treat; LSM, least squares mean; N, number of patients; RCP, randomized control period

Results by treatment week are shown in Table 80 and Figure 37 in Section 16. In each treatment group, the LSM CFB values decreased from Week 2 to Week 6 and increased at Week 8. LSM CFB values were relatively constant in each treatment group after Week 8.

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Proposed Indication for the Treatment of Adult Patients With PNH: Inclusion of C5 Inhibitor Treatment-Naïve and -Experienced Patients

Issue

The Applicant proposed a broad indication: the treatment of adult patients with PNH. This indication includes patients who are C5 inhibitor-naïve and -experienced. The clinical, clinical pharmacology, and pharmacometrics review teams assessed whether the data support the extension of the indication to all patients with PNH, regardless of prior exposure to complement inhibitors.

Background

The Phase 3 trial for this application, Study APL2-302, enrolled 80 patients with PNH previously treated with the C5 inhibitor eculizumab. Two supportive studies, APL2-202 and APL2-204, enrolled patients who were C5 inhibitor-naïve. Study CP0514 enrolled six patients previously treated with eculizumab therapy. Therefore, in total, of the 110 patients in the safety database, 24 patients were C5 inhibitor-naïve with the remainder classified as C5 inhibitor-experienced.

The multidisciplinary review team analyzed the data to determine whether the safety and efficacy provide sufficient support for the inclusion of treatment-naïve patients with PNH in the indication for pegcetacoplan.

Assessment

To determine whether the efficacy and safety data, along with the E-R relationship support the effectiveness of pegcetacoplan for the treatment of patients with PNH who are eculizumab-naïve.

Clinical

The efficacy of pegcetacoplan was similar in C5 inhibitor -naïve and -experienced patients. As discussed in Section 8, there was a statistically significant mean CFB in Hb in both studies with eculizumab-experienced patients (3.84 g/dL at Week 16 in Study APL2-302 and 2.63 g/dL at Week 105 in Cohort 4 of Study CP0514). Similarly, the two supportive studies in patients who were complement inhibitor treatment-naïve also demonstrated an improvement in Hb level after treatment with pegcetacoplan (5.27 g/dL on Day 365 of Study APL2-202 and 3.68 g/dL on Day 365 in Cohort 2 of Study APL2-204). Overall, pegcetacoplan had a similar effect on both patient groups with a positive mean CFB in Hb and improvement in transfusion avoidance and ARC. Despite concerns for the small sample size of treatment-naïve patients, the efficacy findings are consistent for C5 inhibitor-naïve and -experienced patients.

The pathophysiology of PNH involves uncontrolled complement activation, resulting in IVH and EVH. The degree of complement activation may be affected by complement inhibitor therapy; however, the underlying disease pathophysiology is unchanged. Therefore, there is no expected difference in response to pegcetacoplan between C5 inhibitor -naïve and -experienced patients.

PNH is caused by complement-mediated lysis of erythrocyte clones lacking functional glycosylphosphatidylinositol-anchored surface complement regulatory proteins, CD55 and CD59. This renders erythrocytes highly susceptible to the MAC and uncontrolled complement-mediated hemolysis. Uncontrolled complement activation leads to IVH mediated by the C5-dependent MAC and EVH mediated by accumulation of C3 fragments on RBCs and C3b opsonization.

Clinical Pharmacology

Further support for the broad indication comes from E-R analyses of the studies.

In addition to the pivotal Phase 3 Study (APL2-302), the treatment effect of pegcetacoplan was assessed in 24 eculizumab-naïve subjects in Study APL2-204 and Study APL2-202 and 9 eculizumab-treated subjects in Study CP0514, throughout which trough pegcetacoplan concentrations and time-matched Hb levels were measured weekly or biweekly. The PK and efficacy data (Hb and LDH) from these four studies were used for E-R analysis for Hb and LDH response with time-matched pegcetacoplan concentrations.

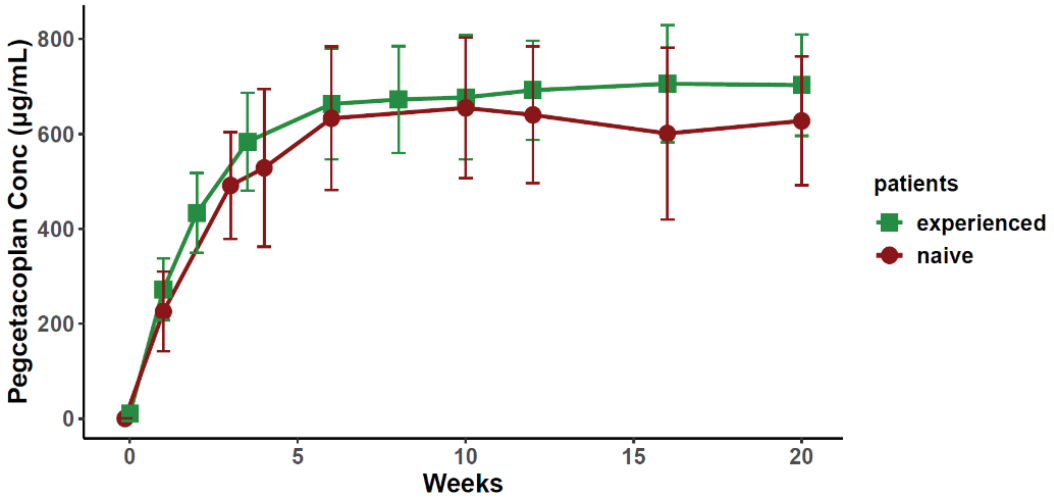
The E-R analysis for Hb response estimated that the Hb E_{max} is a 36.3% increase from baseline and the pegcetacoplan concentration is 272 µg/mL. Prior eculizumab treatment did not affect the E_{max} of Hb or the EC_{50}. Predicted steady-state Hb levels were similar for C5 inhibitor-naïve and -experienced patients (mean ratio 1.07, 90% CI 0.997 to 1.14). Therefore, patients' Hb response to pegcetacoplan is not affected by prior eculizumab treatment.

The E-R relationships for LDH response were different between the eculizumab-treated and -naïve patients, mainly due to their different LDH levels at baseline. Nonetheless, at steady state following the proposed dose of pegcetacoplan, LDH levels are predicted to decrease to 231 IU/L in the naïve patients, comparable to the baseline LDH levels in eculizumab-treated

patients. At the proposed dose, pegcetacoplan exposures are expected to achieve close to the maximal effect for LDH control for both eculizumab-naïve and -experienced patients with PNH.

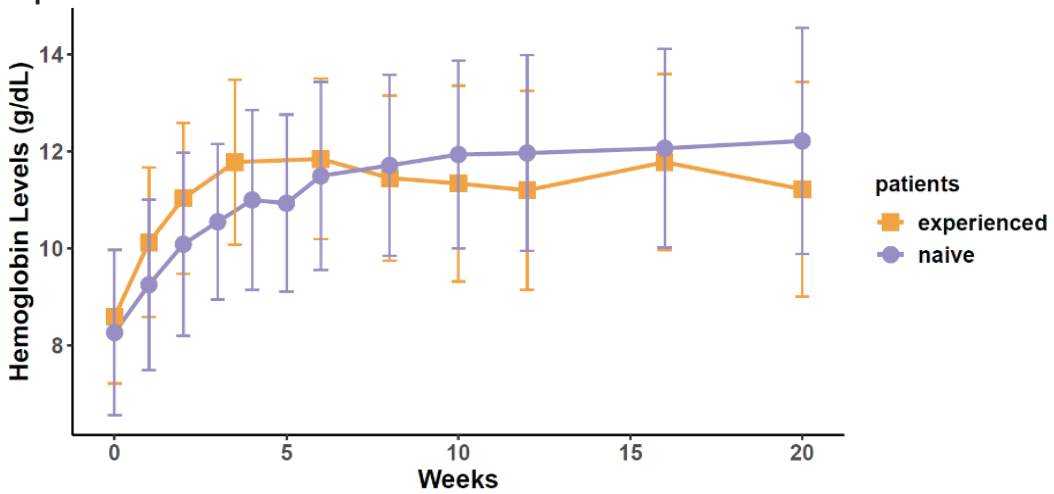
Similarities are also observed in the time courses of observed pegcetacoplan concentrations (Figure 15) and Hb response to pegcetacoplan (Figure 16) between eculizumab-experienced and -naïve patients. These data support broadening of the indication to patients naïve to C5 inhibitor treatment. Note that the C5 inhibitor-naïve patients received a slightly lower dose (270 mg/day) than the experienced patients (approximately 309 mg/day). After 2 weeks of treatment, both experienced and naïve patients had mean pegcetacoplan trough concentrations higher or around 350 µg/mL, which was associated with 80% of the maximum effect on Hb response. Therefore, a loading dose of pegcetacoplan is not critical for achieving a rapid Hb response for either C5 inhibitor -naïve or -experienced patients.

Figure 15. Time Courses of Pegcetacoplan Trough Concentrations in Patients With and Without C5 Inhibitor Experience



Source: Reviewer's analysis.
Abbreviation: conc, concentration

Figure 16. Time Course of Hemoglobin Response in Patients With and Without C5 Inhibitor Experience



Source: Reviewer's analysis.

Exposure-LDH Response

The Applicant's E-R analysis suggests that the E-R relationships for LDH differ between eculizumab-experienced and -naïve patients, mainly driven by the different baseline LDH levels. In the patients who were on eculizumab, LDH was already controlled and initiating treatment of pegcetacoplan further decreased LDH levels by 33%, resulting in a final LDH level of 177 IU/L. In contrast, the LDH levels of patients not on eculizumab were elevated to almost 10-fold the ULN (226 IU/L). Pegcetacoplan reduced the LHD level of naïve patients by 90%, to 231 IU/L. Although the E_{max} differed depending on use of eculizumab at baseline, the EC_{50} estimates were similar for naïve (250 µg/mL) and experienced 173 µg/mL) patients. This suggests that, similar to the Hb response, the proposed dose is expected to provide maximal effects on LDH for both eculizumab-naïve and -experienced patients.

Safety

Overall, the number of reported treatment-emergent adverse events (TEAEs in ≥10% of patients were similar between C5 inhibitor -naïve and -experienced patients. The TEAEs are listed in Table 17.

Table 17. Treatment-Emergent Adverse Events[1] Reported in ≥10% of Patients Treated With Pegcetacoplan, APL2-302

Medical Query[2]	C5 Inhibitor-Naïve[3] N=24 n (%)	C5 Inhibitor-Experienced[4] N=47 n (%)
General disorders and administration site conditions		
Injection site reaction[5]	8 (33.3)	21 (44.7)
Pyrexia[5]	3 (12.5)	8 (17)
Fatigue[5]	1 (4.2)	8 (17)
Infections, all[5]	10 (41.7)	16 (34)
Nasopharyngitis[5]	4 (16.7)	6 (12.8)
Upper respiratory tract infection[5]	8 (33.3)	8 (17)
Viral infection	1 (4.2)	7 (14.9)
Gastrointestinal disorders		
Diarrhea	0 (0)	10 (21.3)
Abdominal pain[5]	2 (8.3)	11 (23.4)
Blood and lymphatic system disorders		
Hemolysis[5]	5 (20.8	4 (8.5)
Dermatologic disorders		
Erythema[5]	6 (25)	6 (12.8)
Vascular disorders		
Hemorrhage[5]	6 (25)	8 (17)
Epistaxis	3 (12.5)	0 (0)
Cardiovascular disorders		
QT prolonged	3 (12.5)	3 (6.4)
White blood cell disorders		
Leukopenia[5]	4 (16.7)	4 (8.5)
Respiratory disorders		
Cough[5]	3 (12.5)	3 (6.4)
Neurologic disorders		
Dizziness	4 (16.7)	3 (6.4)
Investigational laboratory tests		
Got, gpt, ggtp, lfts[5]	3 (12.5)	7 (14.9)

Medical Query[2]	C5 Inhibitor-Naïve[3] N=24 n (%)	C5 Inhibitor-Experienced[4] N=47 n (%)
Metabolism and nutrition disorders		
Hypokalemia	4 (16.7)	5 (10.6)

Source: Clinical data scientist and clinical reviewer.
[1] Treatment-emergent adverse event defined as 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.
[2] Coded as Medical Dictionary for Regulatory Activities preferred terms.
[3] C5 inhibitor-naïve patients: Pooled Study APL2-202 and Cohort 2 of Study APL2-204.
[4] C5 inhibitor-experienced patients: Pooled Study APL2-302 pegcetacoplan group from the RCP and Cohort 4 of Study CP0514.
[5] The following terms were combined:
Abdominal pain includes: abdominal pain upper, abdominal discomfort, abdominal pain, abdominal pain lower, abdominal tenderness, epigastric discomfort
Cough includes: cough, productive cough
Fatigue includes asthenia, lethargy, fatigue
Nasopharyngitis includes: nasopharyngitis, rhinitis, pharyngitis
Got, gpt, ggtp, lfts includes: alanine amino transferase increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, transaminases increased, hepatocellular injury
Injection site reaction includes: injection site erythema, injection site swelling, injection site induration, injection site bruising, injection site pain, injection site pruritus, vaccination site reaction, administration site swelling, injection site hemorrhage, injection site edema, injection site warmth, administration site pain, application site pain, injection site mass, injection site rash, vaccination site pain
Leukopenia includes: febrile neutropenia, neutropenia, neutrophil count decreased, white blood cell count decreased
Pyrexia includes: febrile neutropenia, pyrexia, body temperature increased
Upper respiratory tract infection includes: influenza like illness, nasopharyngitis, rhinitis, pharyngitis, tonsillitis, viral upper respiratory tract infection, upper respiratory tract infection, respiratory tract infection, sinusitis
Viral infection includes: oral herpes, gastrointestinal viral infection, viral upper respiratory tract infection, rhinovirus infection, influenza l ke illness, rhinitis, nasopharyngitis, upper respiratory tract infection
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with adverse event; PT, preferred term; QT, QT interval

Conclusion

Clinical

The clinical, safety, and E-R analyses did not identify a significant difference in Hb response between eculizumab-treated and -naïve patients. The underlying disease pathophysiology is the same for individuals with PNH, irrespective of whether they have been previously treated with complement inhibitor therapy.

In summary, therefore, the efficacy and safety data support the proposed indication for the treatment of adults with PNH. A postmarketing requirement will be issued in order to obtain additional long-term safety data, and specifically data in treatment-naïve patients, which constituted a small proportion of the patients in this application.

6.3.2. Acceptability of Extending Inclusion Criteria to Include Patients Treated With Any Approved C5 Inhibitor Therapies

Issue

The active comparator for Study APL-302 was eculizumab. The clinical and clinical pharmacology review teams assessed whether the safety, efficacy, and clinical pharmacology data would support the transition from all approved C5 inhibitor therapies, including ravulizumab-cwvz, to pegcetacoplan.

Background

At the start of the Phase 3 trial, Study APL2-302, eculizumab was the only approved therapy for the treatment of adult patients with PNH; therefore, it was used as the active comparator. Eculizumab is administered IV, with weekly dosing (600 mg) for the first 4 weeks followed by a fifth dose (900 mg) 1 week later, then 900 mg every 2 weeks thereafter. Since the start of Study APL2-302, a second C5 inhibitor, ravulizumab-cwvz, was approved for the treatment of adult patients with PNH. Ravulizumab-cwvz, like eculizumab, binds C5 and blocks its activation, preventing the formation of C5a and the formation of the terminal C5b-9 MAC, thus antagonizing terminal complement activity. Ravulizumab-cwvz is a longer-acting C5 inhibitor administered as an IV loading dose, with maintenance dosing at 8-week intervals.

Assessment

Ravulizumab-cwvz dosing has been studied in patients with PNH and atypical hemolytic uremic syndrome to achieve optimized therapeutic steady-state concentrations following the first dose, resulting in immediate onset of action and complete terminal complement inhibition by the end of the first infusion. The serum half-life yields prolonged pharmacologic activity, allowing dosing once every 4 weeks and once every 8 weeks. This sustained C5 inhibition has been confirmed in PNH trials (Kulasekararaj et al. 2019; Lee et al. 2019).

Conclusion

A multidisciplinary decision that involved the Clinical and Clinical Pharmacology review teams determined that as ravulizumab-cwvz is a derivative of eculizumab and results in similar demonstration of inhibition of C5. Therefore, patients with PNH should have similar results transitioning from either approved C5 inhibitor therapy to pegcetacoplan. To account for the difference in frequency of administration with C5 inhibitor therapy, Section 2.2 of the United States Prescribing Information has been amended to state that for patients switching from ravulizumab-cwvz, pegcetacoplan should be administered (b) (4) after the last dose of ravulizumab-cwvz.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Toxicological characterization of pegcetacoplan was assessed in monkeys dosed up to 9 months and in rabbits dosed up to 6 months. Assessment in monkeys reflects both on- and off-target effects of pegcetacoplan, whereas the rabbit studies reflect primarily off-target effects. Reproductive toxicology was assessed in an enhanced pre- and postnatal development study in cynomolgus monkeys. Carcinogenicity studies were not conducted because pegcetacoplan is not pharmacologically active in rodents. Notable toxicities of potential clinical interest are discussed below.

Reproductive Toxicity Findings

Pregnant cynomolgus monkeys injected subcutaneously with 7 and 28 mg/kg pegcetacoplan from gestation Day 20/22 until parturition had significantly increased frequencies of stillbirths and abortions at 28 mg/kg. The no observed adverse effect level (NOAEL) for abortions and stillbirths was 7 mg/kg (1.3× the maximum recommended human dose). The incidences of infant loss with pegcetacoplan and the historical range for cynomolgus monkeys from the facility conducting the study are shown in Table 18.

Table 18. Infant Loss and Mortality in Cynomolgus Monkeys

Pegcetacoplan Dose	Infants Born	Percentages of Stillbirths and Abortions
0 mg/kg	19	5%
7 mg/kg	17	10.5%
28 mg/kg	9	52.6%
Historical range (control)	-	6.7 to 38.9%

Source: Study report 18CATX-001.

There was no evidence of underlying maternal toxicity or of fetal and infant malformations associated with the abortions and stillbirths. There was no evidence of neurobehavioral changes in surviving infants exposed to maternal pegcetacoplan. Analysis of milk, placenta, and fetal blood demonstrated exposure to pegcetacoplan, but the concentrations were a fraction (<1%) of the maternal serum levels. The study did not have a PEG-40 control to determine whether PEG-40 had played a role in increased stillbirths and abortions. The cause of the increased frequency of abortions/stillbirths at 28 mg/kg pegcetacoplan is unknown and occurs at a low multiple of clinical exposure (2.9× the clinical area under the concentration-time curve [AUC]); therefore, a clinical risk of an AE of pegcetacoplan on pregnancy outcomes cannot be excluded.

PEG-40–Related Vacuolation

Daily SC administration of pegcetacoplan to monkeys for up to 9 months and to rabbits for up to 6 months caused renal tubular degeneration and vacuolated histiocytic infiltrates and epithelia of the brain choroid plexus. Vacuolation of infiltrating or resident macrophages and occasionally epithelial cells was observed seen in other tissues (e.g., cervix, injection sites, adrenal gland, liver, lymph nodes, ovary, bone marrow, and urinary bladder).

The vacuolation of tissues observed with PEGylated pharmaceuticals is generally considered an adaptive response intended to clear PEG-40 from the circulation, rather than being a toxicological process (Ivens et al. 2015). However, the choroid plexus epithelia and kidney tubular epithelia were considered of most clinical interest for potential adverse changes secondary to PEG accumulation. As discussed below, these vacuolations were driven by PEG-40, which constitutes (b) (4)% of total pegcetacoplan by weight, and not by the active peptide moiety. The severity and incidence of vacuolations were consistent between the highest dose of pegcetacoplan (28 mg/kg) and the matching PEG-40 control group in these studies.

Renal Tubular Degeneration and Vacuolation

Renal tubular degeneration of minimal severity was observed at 28 mg/kg pegcetacoplan (2.9× the clinical dose based on AUC) in both rabbits and monkeys (Table 19). The minimal severity of renal tubular degeneration generally did not change from 1 month to chronic dosing of 28 mg/kg pegcetacoplan, indicating an absence of lesion progression with duration, but did not

reverse following a 28-day recovery phase. The cause of renal tubular degeneration is unknown, but likely relates to the PEG-40 component of pegcetacoplan because it was also observed in the PEG-40 control group. Similarly, the incidence and severity of tubular vacuolation were similar between pegcetacoplan and the PEG-40 control, identifying cellular uptake of PEG-40 as a causative factor. Vacuolation and tubular degeneration generally coincided in both species; however, a causative association was not definitively established. The renal tubular degeneration occurred in monkeys at 28 mg/kg, or 2.9× the clinical dose based on AUC, and ~5.4× relative to PEG exposure. The NOAEL for renal tubular degeneration was at 7 mg/kg with a 1.4-fold safety margin, supporting the renal safety of clinically relevant exposure to pegcetacoplan.

Table 19. Renal Histopathology Findings in 9-Month Monkey and 6-Month Rabbit Studies With Pegcetacoplan

SC Dose	Pegcetacoplan				PEG-40	Pegcetacoplan				PEG-40
(mg/kg/day)	0	1	7	28	26	0	1	7	28	26
Finding	Cynomolgus Monkeys					Rabbits				
Number with kidney tubular degeneration, minimal	0 M 1 F	0 M 0 F	0 M 0 F	2 M 4 F	0 M 1 F	0 M 2 F	0 M 4 F	1 M 4 F	2 M 6 F	3 M 3 F
Number with kidney tubular vacuolization, minimal	0 M 0 F	0 M 0 F	1 M 0 F	5 M 5 F	3 M 4 F	0 M 0 F	1 M 5 F	4 M 6 F	6 M 1 F	6 M 5 F
Number with kidney tubular vacuolation, mild	0 M 0 F	0 M 0 F	0 M 0 F	0 M 0 F	0 M 0 F	0 M 0 F	0 M 0 F	0 M 0 F	0 M 4 F	0 M 1 F

Source: Study Report 15CATX-004, Table 5 and Study Report 15CATX-003, Table 5.
Six animals per sex per group in the monkey study and the rabbit study.
Abbreviations: F, female; M, male; n, number; PEG, polyethylene glycol; SC, subcutaneous

Vacuolation of the Brain Choroid Plexus

Minimal to moderate vacuolations of histiocytic macrophages (infiltrate and resident) and epithelial cells in the brain choroid plexus were observed with pegcetacoplan and the matching PEG-40 control in both monkeys and rabbits (Table 20), suggesting that cellular vacuolations were driven by the PEG-40 component.

Table 20. Brain Vacuolations in 9-Month Monkey and 6-Month Rabbit Studies With Pegcetacoplan

SC Dose	Pegcetacoplan				PEG-40	Pegcetacoplan				PEG-40
(mg/kg/day)	0	1	7	28	26	0	1	7	28	26
Finding	Cynomolgus Monkeys					Rabbits				
Number with brain choroid plexus vacuolations, minimal	0 M 0 F	4 M 0 F	0 M 3F	0 M 0 F	0 M 0 F	0 M 0 F	0 M 0 F	4 M 0 F	2 M 0 F	0 M 0 F
Number with brain choroid plexus vacuolations, mild	0 M 0 F	0 M 0 F	5 M 3 F	0 M 0 F	0 M 0 F	0 M 0 F	0 M 0 F	0 M 3 F	0 M 0 F	0 M 0 F
Number with brain choroid plexus vacuolations, moderate	0 M 0 F	0 M 0 F	1 M 0 F	6 M 6 F	6 M 6 F	0 M 0 F	0 M 0 F	0 M 3 F	6 M 6 F	6 M 6 F

Source: Source: Study Report 15CATX-004, Table 5 and Report 15CATX-003, Table 5.
Six animals per sex per group in the monkey study and the rabbit study.
Abbreviations: F, female; M, male; n, number; PEG, polyethylene glycol; SC, subcutaneous

Vacuolations of choroid plexus and multiple other tissues have been observed with other PEGylated products in animals with the primary concern being whether these vacuolations eventually result in structural changes that affect tissue/organ function. Fletcher et al. (2019)

reports that adverse changes to tissue architecture occurred in the choroid plexus of monkeys at 3 months following a weekly PEG-40 load of ≥160 mg/kg but not ≤ 120 mg/kg, suggesting that there is a threshold at which accumulation of cellular PEG may become adverse. Monkeys administered 7 and 28 mg/kg/day pegcetacoplan were exposed to a weekly PEG-40 load of ~44 mg/kg and 176 mg/kg, respectively, which approximates to 1.4- and 5.4-fold multiples of human exposure to PEG-40 from the clinical dose of pegcetacoplan. Vacuolation of the choroid plexus epithelium was observed at a similar incidence at both doses but with greater severity (to moderate) at the higher 28 mg/kg dose. There was no reported evidence of disrupted tissue structure (e.g., degeneration/regeneration, necrosis, hyperplasia, interstitial expansion) of the choroid plexus itself or of the surrounding vasculature and brain tissue at either dose at 9 months in monkeys. There was also no adverse clinical sign indicative of neurobehavioral disruption, at least from routine observation in the pivotal toxicology studies. Though not evaluated in the toxicology studies, pegcetacoplan was below detectable levels in the central nervous system following a single SC administration to monkeys in a tissue distribution study. A more robust evaluation would have included a directed neurobehavioral exam and evaluation of PEG in brain tissue (e.g., histochemistry) and in cerebral spinal fluid from the chronic study in monkeys, particularly at the highest dose administered (28 mg/kg). Nonetheless, at clinically relevant exposure to pegcetacoplan, there is no evidence that vacuolation of the choroid plexus epithelium and attendant histiocytic cells resulted in histological or clinical signs of an AE in the chronic toxicology studies.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The potential safety concerns were reviewed based on known information for the approved C5 inhibitor therapies and literature on patients with hereditary C3 deficiency. The Warnings and Precautions for pegcetacoplan include serious infections caused by encapsulated bacteria. AEs of special interest for pegcetacoplan in Study APL2-302 included injection site reactions, infection, thrombosis, hypersensitivity, and hemolysis.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Pegcetacoplan is not approved or marketed in the United States or worldwide.

7.4. FDA Approach to the Safety Review

Safety Review Approach

The Applicant's safety database consisted of four completed studies. The safety population consisted of patients or subjects who received at least one dose of pegcetacoplan. The primary safety population comprised 80 patients with PNH from Study APL2-302.

The data cutoff date for the primary PNH safety database was May 31, 2020. In addition, the Applicant submitted a 120-day safety update and a 48-week summary for Study APL2-302. Supportive safety data consisted of three completed studies in adult patients with PNH in Study APL2-202, APL2-CP-PNH-204 (Study APL2-204) Cohort 2, and CP0514 (Study CP0514)

Cohort 4. As of the data cutoff date, there were three ongoing studies of pegcetacoplan in patients with PNH: Study APL2-302 open-label phase, Study APL2-307, and APL2-308.

The clinical review of safety for this New Drug Application is based on the following:

- Protocols for the studies listed above
- Data sets for the populations described above
- Summary of clinical safety
- 120-day safety update
- APL2-302 48-week summary
- Patient narratives
- Case report forms

Case report forms and narratives were provided and reviewed for AEs of interest, serious adverse events (SAEs), and deaths that occurred in the primary and supportive safety populations.

The ADAE.xpt data file was reviewed for accuracy of translation of the verbatim to preferred term (PT) by manual review. Based on this review, a modified table was produced to which additional PTs were added based on the verbatim term. With additions of PTs, the AE file was copied with the new PTs. Similar PTs were grouped by standardized groupings of related PTs using Food and Drug Administration medical queries.

The safety data submitted were well organized and relevant data were easily identified. The Applicant provided all clinical datasets with the initial submission. The Applicant provided sufficient safety information on patients enrolled in Studies APL2-302, APL2-202, APL2-204, and CP0514, including full datasets and narratives of deaths, SAEs, or TEAEs leading to permanent discontinuation of study treatment.

Safety Analysis Plan and Definitions

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 20.0 and presented by system organ class and PT. AEs were graded according to the National Cancer Institute–Common Terminology Criteria for Adverse Event, version 4.03. TEAEs were defined as those AEs that occurred after dosing on Day -28 or worsened in severity. AEs that did not meet the TEAE criteria were classified as pretreatment AEs.

Based on specific AEs previously observed across complement inhibitor drugs, as well as disease morbidities, the Applicant identified several AEs of special interest, including serious infections with encapsulated bacteria, infusion reactions, thrombosis, hemolytic disorders, and hypersensitivity reactions.

The Applicant defined an SAE as any AE or suspected adverse reaction that in the view of either the investigator or the Applicant, resulted in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, and/or a congenital anomaly/birth defect.

The ADAE.xpt datafile was reviewed for accuracy of translation from verbatim to PTs by manual review. All translations of AE term to AE code were complete.

Routine Clinical Tests

Safety assessments included physical examinations, vital signs, laboratory measurements including a complement panel and flow cytometry for PNH and C3 deposition, electrocardiogram (ECG) parameters, and FACIT-F fatigue score. Vaccination history was obtained on Days -4, -3, and -2 of the run-in period, in addition to Day 2 of the RCP.

7.5. Adequacy of the Clinical Safety Database

The safety database of the adult PNH safety population represents a patient population consistent with the demographics and disease characteristics of PNH. Most patients were from Europe and the United States. Although the safety database is small, safety can be adequately assessed. Given the rarity of the disease, the patient exposure appears to be adequately representative of the to-be-marketed U.S. patient population.

A total of 110 patients with PNH has been exposed to systemic pegcetacoplan up to the data cutoff date of May 21, 2020. In the entire safety population, the median duration of treatment was 10.8 months (range 1 to 28.1 months). A summary of exposure for all studies submitted in adult patients with PNH is shown in Table 21.

Table 21. Pegcetacoplan Exposure in the Safety Populations

Parameter	APL2-302 Run-In Period PGC 1,080 mg BIW+ECU N=80 n (%)	APL2-302 RCP PGC 1,080 mg BIW N=41 n (%)	APL2-302 RCP ECU N=39 n (%)	APL2-202 PGC 270 mg QD N=4 n (%)	APL2-204 PGC 270 mg QD N=20 n (%)	APL2-CP-0514 PGC 270 mg QD N=6 n (%)
Duration of treatment (months)						
Mean (SD)	4.5 (0.4)	4.4 (0.6)	4.5 (0.2)	12.1 (0.1)	13.3 (4.7)	22 (7.6)
Median	4.6	4.6	4.6	12.1	14.6	24.3
(min, max)	(2.1, 4.7)	(2.1, 4.7)	(3.7, 4.7)	(12, 12.2)	(1, 18.9)	(6.8, 28.1)
Patients treated, by duration, n (%)						
<3 months	3 (3.8)	3 (7.3)	0 (0)	0 (0)	2 (10)	0 (0)
≥3 to 6 months	77 (96.2)	38 (92.7)	39 (100)	0 (0)	0 (0)	0 (0)
≥6 to <12 months	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)
≥12 to <24 months	0 (0)	0 (0)	0 (0)	4 (100)	18 (90)	1 (16.7)
≥24 to <36 months	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (66.7)
≥36 months	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Source: Derived from the Applicant's SCS.
Abbreviations: BIW, twice a week; ECU, eculizumab; max, maximum; min, minimum; N, number of subjects in group; n, number of subjects with given treatment duration; PGC, pegcetacoplan; QD, daily; RCP, randomized control period; SCS, summary of clinical safety; SD, standard deviation

The overall extent of exposure for patients in the primary safety population (n=80) is summarized in Table 22. This included 80 subjects who received concomitant pegcetacoplan and eculizumab therapy during the run-in period of Study APL2-302, and were randomized to pegcetacoplan (N=41) or eculizumab (N=39) in the RCP. In the primary safety population, the median duration of treatment during the run-in period was 4.6 months (range 2.1 to 4.7 months). The combined median pegcetacoplan treatment duration for all patients during the RCP was 4.6 months (range 2.1 to 4.7 months).

Table 22. Total Exposure for the Primary PNH Safety Population

Parameter	APL2-302 Run-In Period PGC 1,080 mg BIW+ECU N=80 n (%)	APL2-302 RCP PGC 1,080 mg BIW N=41 n (%)	APL2-302 RCP ECU N=39 n (%)	APL2-302 RCP PGC 1,080 mg BIW+ECU N=80 n (%)
Duration of treatment (months)				
Mean (SD)	4.5 (0.4)	4.4 (0.6)	4.5 (0.2)	4.5 (0.4)
Median	4.6	4.6	4.6	4.6
(min, max)	(2.1, 4.7)	(2.1, 4.7)	(3.7, 4.7)	(2.1, 4.7)
Patients treated, by duration, n (%)				
<3 months	3 (3.8)	3 (7.3)	0 (0)	3 (3.8)
≥3 to 6 months	77 (96.2)	38 (92.7)	39 (100)	76 (96.2)
≥6 to <12 months	0 (0)	0 (0)	0 (0)	0 (0)
≥12 to <24 months	0 (0)	0 (0)	0 (0)	0 (0)
≥24 to <36 months	0 (0)	0 (0)	0 (0)	0 (0)
≥36 months	0 (0)	0 (0)	0 (0)	0 (0)

Source: Derived from the Applicant's SCS.
Abbreviations: BIW, twice a week; ECU, eculizumab; max, maximum; min, minimum; N, number of subjects in group; n, number of subjects with given treatment duration; PGC, pegcetacoplan; PNH, paroxysmal nocturnal hemoglobinuria; QD, daily; RCP, randomized control period; SCS, summary of clinical safety; SD, standard deviation

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

The demonstrated safety profile of pegcetacoplan in patients with PNH is acceptable at the indicated dose. In Study APL2-302, injection site reactions, infection, diarrhea, and abdominal pain were the most common adverse reactions. There were no deaths in Study APL2-302. Discontinuations were due to hemolysis.

The Safety Update Report described AEs that occurred during the 120 Days following the Week 16 data cutoff. The reported AEs were similar to those that occurred during the RCP and no new safety signals were identified. Events included enterococcal bacteremia, vitreitis, and pyrexia. There were no events that changed the reviewer's opinion about the benefit/risk assessment of pegcetacoplan for the treatment of adult patients with PNH.

7.6.1. Safety Findings and Concerns, APL2-302

7.6.1.1. Overall Treatment-Emergent Adverse Event Summary, APL2-302

Grading was based on the National Cancer Institute–Common Terminology Criteria for Adverse Event criteria. AEs were graded as 1, mild; 2, moderate; or ≥3, severe. The majority of patients experienced AEs that were grade 1 or grade 2 in severity, as shown in Table 23.

Table 23. Overview of TEAEs,[1] Controlled Trial Safety Population, APL2-302

Event	Run-In Period PGC+ECU N=80 n (%)	RCP PGC N=41 n (%)	RCP ECU N=39 n (%)
Any TEAE	69 (86.2)	36 (87.8)	34 (87.2)
Moderate or severe (grade 3-4) AEs	2 (2.5)	8 (19.5)	5 (12.8)
SAEs	1 (1.3)	7 (17.1)	6 (15.4)
SAEs with fatal outcome	0 (0)	0 (0)	0 (0)
AEs leading to discontinuation of study drug	0 (0)	3 (7.3)	0 (0)
AEs leading to dosage modification of study drug	1 (1.2)	1 (2.4)	0 (0)
AEs leading to interruption of study drug	1 (1.2)	1 (2.4)	0 (0)
AEs leading to reduction of study drug	0 (0)	0 (0)	0 (0)
AEs leading to dosage delay of study drug	0 (0)	0 (0)	0 (0)

Source: adae xpt; software: Python.
[1] Treatment-emergent adverse event defined as 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.
If more than one AE with the same PT was reported before the date of the first dose, then the AE with the greatest severity was presented in summaries. An AE that occurred more than 30 Days after the date of the last dose was not counted as a TEAE.
Grading scale: Mild, moderate and severe.
Study APL2-302 RC period PGC+ECU group treatment-emergent adverse event was defined as an adverse event that occurred after the randomization date but before the first monotherapy and is summarized under the PGC+ECU group.
Study APL2-302 duration was 16 weeks.
Abbreviations: AE, adverse event; ECU, eculizumab; N, number of subjects in treatment group; n, number of subjects with at least one of the specified event; PGC, pegcetacoplan; SAE, serious adverse event; TEAE, treatment-emergent adverse event

In total, 36 of 41 (87.8%) of patients receiving pegcetacoplan monotherapy during the RCP experienced a TEAE, with 8 of 41 (19.5%) experiencing a grade 3 or 4 TEAE. This is similar to patients receiving eculizumab monotherapy, of whom 34 of 39 (87.2%) experienced a TEAE. Five of 39 (12.8%) subjects receiving eculizumab monotherapy during the RCP experienced a grade 3 or 4 TEAE. In general, there were fewer TEAEs and SAEs during the run-in period compared with the RCP.

7.6.1.2. Deaths in Completed PNH Studies

There were no deaths reported in the pivotal trial APL2-302 during the run-in period or the RCP. Three deaths occurred in the completed supportive PNH studies, two of which were on-study. The events leading to death are described in the following sections.

Study APL2-204

In Study APL2-204, two deaths were reported in Cohort 2:

- Subject (b) (6): A 45-year-old male had a fatal SAE of aplastic anemia and died 56 Days after discontinuation of pegcetacoplan treatment. The patient had no reported medical history of aplastic anemia. Blood samples obtained at the Day 365 study visit revealed severe thrombocytopenia and neutropenia. The subject was admitted to the hospital for investigations and bone marrow aspiration was consistent with aplastic anemia on the background of PNH.
- Subject (b) (6): A 61-year-old female died 22 weeks after discontinuing pegcetacoplan treatment and 17 weeks after discontinuing from the study. The patient withdrew from the study due to a severe SAE of abdominal neoplasm. This death occurred when the patient was no longer enrolled in the study and therefore was not included in the clinical database for the study.

Study CP0514

In Study CP0514, one death was reported for a subject in Cohort 1. This subject was not part of the safety analysis as defined above; however, a description of the event is included as part of the evaluation of the safety of pegcetacoplan.

- Subject (b) (6): A 72-year-old female had an SAE of intracranial hemorrhage with death 34 days after a single 25 mg dose of pegcetacoplan. The patient had a history of aplastic anemia, hypertension and thrombocytopenia. On Day 34, the patient lost consciousness and was admitted to hospital, where evaluations were consistent with brain death.

There was one death reported during the open-label phase of Study APL2-302 that occurred after Week 16 and was therefore not included in the Study APL2-302 clinical study report. Subject (b) (6) had a fatal SAE of coronavirus disease-2019.

7.6.1.3. Serious Adverse Events, APL2-302

In total, 1 of 80 (1.2%) patients in the primary safety population experienced a treatment-emergent SAE during the run-in period of Study APL2-302 from Day -22 to Day -15. The narrative is provided below:

- Subject (b) (6): A 53-year old male with chronic kidney disease was hospitalized with sepsis of unknown etiology. The patient responded to ceftriaxone and was discharged after a 7-day hospitalization. Pegcetacoplan and eculizumab treatment were not changed due to an event of sepsis.

During the RCP of APL2-302, two SAEs occurred in the study period prior to monotherapy. These events were hemolytic anemia and viral upper respiratory tract infection, which are not captured in the table below. After beginning monotherapy in the RCP, 7 of 41 (17.1%) patients in the pegcetacoplan group and 6 of 29 (15.4%) patients in the eculizumab group experienced SAEs. Treatment-emergent SAEs (including groupings of closely related AEs) are shown in Table 24. The most common type of treatment-emergent SAE in the pegcetacoplan group of the RCP was infection in 2 of 41 (4.9%) of patients, which included bacterial infection and gastroenteritis. Hemolysis occurred in 2 of 41 (4.9%) patients receiving pegcetacoplan

monotherapy in the RCP, which included hemolysis and hemolytic anemia. Comparatively, 3 of 39 (7.7%) of patients receiving eculizumab therapy experienced hemolysis. One SAE of facial paralysis in the pegcetacoplan monotherapy group of the RCP was not captured by medical query terms.

Table 24. Treatment-Emergent Serious Adverse Events, Safety Population, APL2-302

Serious Adverse Event[1]	Run-In PGC+ECU N=80 n (%)	RCP PGC N=41 n (%)	RCP ECU N=39 n (%)
Infection, all[2]	1 (1.2)	2 (4.9)	0 (0)
Bacterial infection	0 (0)	1 (2.4)	0 (0)
Gastroenteritis	0 (0)	1 (2.4)	0 (0)
Sepsis	1 (1.2)	0 (0)	0 (0)
Hemolysis[2]	0 (0)	2 (4.9)	0 (0)
Anemia[2]	0 (0)	0 (0)	3 (7.7)
Hyperbilirubinemia, jaundice	0 (0)	0 (0)	1 (2.6)
Abdominal pain	0 (0)	0 (0)	1 (2.6)
Hepatic injury	0 (0)	0 (0)	1 (2.6)
Pyrexia[2]	0 (0)	1 (2.4)	2 (5.1)
Dyspnea	0 (0)	1 (2.4)	0 (0)
Atrial fibrillation	0 (0)	1 (2.4)	0 (0)

Source: Clinical data scientist and FDA reviewer.
[1] Coded as FDA Medical Queries.
[2] The following terms were combined:
Anemia includes hemolytic anemia, anemia
Hemolysis includes hemolysis, hemolytic anemia
Infection, all includes bacterial infection, gastroenteritis, sepsis
Pyrexia includes pyrexia, hyperthermia
Abbreviations: ECU, eculizumab; N, number of subjects in group; n, number of subjects with specified adverse event; PGC, pegcetacoplan; RCP, randomized control period

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events, APL2-302

There were no TEAEs leading to study discontinuation or study drug discontinuation during the run-in period. During the RCP, three patients in the pegcetacoplan group experienced one SAE and two TEAEs of hemolysis that led to study drug discontinuation. One of those subjects discontinued from the study. Table 25 summarizes these discontinuations.

Table 25. Adverse Events Leading to Discontinuation, Safety Population, APL2-302

Adverse Event[1]	Run-In Period PGC+ECU N=80 n (%)	RCP PGC N=41 n (%)
Patients with at least one AE leading to discontinuation of study drug	0 (0)	3 (7.3)
Hemolysis	0 (0)	3 (7.3)

Source: Clinical data scientist and FDA clinical reviewer.
[1] Coded as Medical Dictionary for Regulatory Activities preferred terms.
Abbreviations: AE, adverse event; ECU, eculizumab; N, number of subjects in group; n, number of subjects with adverse event; PGC, pegcetacoplan; RCP, randomized control period

7.6.1.5. Treatment-Emergent Adverse Events, APL2-302

In total, 69 of 80 (86.2%) of patients experienced a TEAE during the run-in period of Study APL2-302. The most common TEAE during the run-in period was injection site reaction, in 44 of 80 (55%) patients. Infections, diarrhea, abdominal pain, viral infection, fatigue, respiratory

tract infection, and back pain were the TEAEs reported in more than one patient during the run-in period of Study APL2-302.

During monotherapy of the RCP, 36 of 41 (87.8%) of patients receiving pegcetacoplan experienced a TEAE. The most common type of TEAE in the pegcetacoplan group during the RCP was injection site reaction, in 16 of 41 (39%) patients. Infections were the second most common TEAE, seen in 12 of 41 (29.3%) of patients. Diarrhea, abdominal pain, respiratory tract infection, and viral infection were frequent TEAEs reported in more than one patient in the pegcetacoplan group of the RCP.

Thirty-four of thirty-nine (87.2%) patients receiving eculizumab monotherapy during the RCP experienced a TEAE. The most frequently reported TEAEs in patients receiving eculizumab during the RCP were infections, reported in 10 of 39 (25.6%) patients followed by hemolysis reported in 11 of 39 (28.2%) patients. Fatigue, respiratory tract infection, abdominal pain and back pain were frequently reported TEAEs in patients receiving eculizumab monotherapy. The frequencies of TEAES are shown in Table 26.

Table 26. Treatment-Emergent Adverse Events[1] Reported in ≥5% of Patients Treated With Pegcetacoplan, APL2-302

Adverse Event[2]	Run-In Period PGC+ECU N=80 n (%)	RCP PGC N=41 n (%)	RCP ECU N=39 n (%)
General disorders and administration site conditions			
Injection site reaction[3]	44 (55.0)	16 (39.0)	2 (5.1)
Fatigue[3]	3 (3.8)	5 (12.2)	9 (23.1)
Chest pain[3]	3 (3.8)	3 (7.3)	1 (2.6)
Infections, all[3]	11 (13.8)	12 (29.3)	10 (25.6)
Respiratory tract infection[3]	4 (5)	6 (14.6)	5 (12.8)
Viral infection[3]	5 (6.2)	5 (12.2)	3 (7.7)
Gastrointestinal disorders			
Diarrhea	6 (7.5)	9 (22.0)	1 (2.6)
Abdominal pain[3]	6 (7.5)	8 (19.5)	4 (10.3)
Blood and lymphatic system disorders			
Hemolysis[3]	1 (1.2)	4 (9.8)	11 (28.2)
Musculoskeletal disorders			
Back pain[3]	4 (5.0)	3 (7.3)	4 (10.3)
Cardiovascular disorders			
Systemic hypertension[3]	0 (0)	3 (7.3)	1 (2.6)

Source: Clinical data scientist and FDA clinical reviewer.
[1] Treatment-emergent adverse event: 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.
[2] Coded as Medical Dictionary for Regulatory Activities preferred terms
[3] The following terms were combined:
Abdominal pain includes: abdominal pain upper, abdominal discomfort, abdominal pain, abdominal pain lower, abdominal tenderness, epigastric discomfort
Back pain includes: back pain, sciatica
Chest pain includes: chest discomfort, noncardiac chest pain, musculoskeletal chest pain, chest pain
Fatigue includes: asthenia, lethargy, fatigue
Hemolysis includes: hemolysis, hemolytic anemia, hemoglobinuria
Infections include: oral herpes, bacterial infection, fungal infection, gastrointestinal infection, gastrointestinal viral infection, influenza like illness, nasopharyngitis, pulpitis dental, rhinitis, tonsillitis, tonsillitis bacterial, vulvovaginal mycotic infection, hordeolum, sepsis, furuncle, otitis externa, viral respiratory tract infection, gastroenteritis, upper respiratory tract infection, bronchitis, ear infection, respiratory tract infection, rhinovirus infection, sinusitis, urinary tract infection
Injection site reaction includes: injection site erythema, injection site reaction, injection site swelling, injection site induration, injection site bruising, injection site pain, injection site pruritus, vaccination site reaction, administration site swelling, injection site hemorrhage, injection site edema, injection site warmth, administration site pain, application site pain, injection site mass, injection site rash, vaccination site pain
Respiratory tract infection includes: influenza like illness, nasopharyngitis, rhinitis, tonsillitis, viral upper respiratory tract infection, upper respiratory tract infection, respiratory tract infection, sinusitis
Systemic hypertension includes: hypertension
Viral infection includes: oral herpes, gastrointestinal viral infection, viral upper respiratory tract infection, rhinovirus infection
Abbreviations: CI, confidence interval; ECU, eculizumab, N, number of subjects; n, number of subjects with adverse event; PGC, pegcetacoplan; PT, preferred term; RCP, randomized control period

Eighteen patients had an AE of abdominal pain during the run-in period or RCP of Study APL2-302, including eight patients randomized to the pegcetacoplan group and seven patients randomized to the eculizumab group. Six of the eighteen patients had a concomitant event of gastroenteritis, diarrhea, or an AE in the system organ class of gastrointestinal disorders, two in the run-in period and five in the RCP with one patient having an event in both the run-in period and RCP. Of these six patients, two had events during the run-in period while on pegcetacoplan and eculizumab combination therapy, one had an event while on eculizumab monotherapy, and four had events on pegcetacoplan monotherapy. The concomitant events included diarrhea (three patients), nausea (two patients), dyspepsia, abdominal distension, and flatulence (one patient each). Of the 18 patients who had an AE reported of abdominal pain during the run-in period or

RCP of Study APL2-302, 3 had a concomitant event of hemolysis; 2 in the eculizumab group and 1 in the pegcetacoplan group of the RCP. Overall, in this subset of subjects who reported abdominal pain during the study, the mean baseline LDH values were within the normal range.

7.6.1.6. Adverse Events of Special Interest, APL2-302

Infections

Patients enrolled in Study APL2-302 were monitored for infections and vaccinated against encapsulated organisms (*N. meningitidis, H. influenzae, S. pneumoniae*). If a patient was not already vaccinated, vaccination was performed 14 days prior to study drug administration during the screening period. In addition to vaccination, prophylactic antibiotic therapy was administered at the discretion of the treating investigator in accordance with local treatment guidelines for patients with PNH who are receiving treatment with a complement inhibitor.

Infections were a common TEAE in Study APL2-302. During the run-in period, infections occurred in 11 of 80 (14%) patients. During the RCP, 12 of 41 (29%) patients in the pegcetacoplan group experienced a TEAE of infection compared with 10 of 39 (26%) in the eculizumab group. The most common infections experienced by patients receiving pegcetacoplan during the RCP were respiratory tract infections, which occurred in 6 of 41 (15%) patients. This FDA medical query included PTs such as influenza-like illness, nasopharyngitis, and viral upper respiratory tract infection. There were no reported serious infections with encapsulated bacteria, including meningococcal infection, during the run-in or RCP of Study APL2-302. One patient developed sepsis during the run-in period, which is described as an SAE in Section 6.3. One patient in the pegcetacoplan group of the RCP developed an infection with an unidentified bacterial pathogen. The patient narrative is provided in Section 6.3. All infections in the primary safety population are listed in Table 27.

Table 27. All Infections in the Primary Safety Population, APL2-302

Infection Type[1]	Run-In Period PGC+ECU N=80 n (%)	RCP PGC N=41 n (%)	RCP ECU N=39 n (%)
Infections, all[2]	11 (13.8)	12 (29.3)	10 (25.6)
Upper respiratory tract infection[2]	4 (5)	6 (14.6)	5 (12.8)
Viral infection[2]	5 (6.2)	5 (12.2)	3 (7.7)
Herpes virus[2]	2 (2.5)	2 (4.9)	0 (0)
Bacterial infection[2]	0 (0)	2 (4.9)	0 (0)
Fungal infection[2]	1 (1.2)	2 (4.9)	0 (0)
Nasopharyngitis[2]	0 (0)	1 (2.4)	0 (0)
Urinary tract infection	1 (1.2)	0 (0)	2 (5.1)
Furuncle	1 (1.2)	0 (0)	0 (0)
Sepsis	1 (1.2)	0 (0)	0 (0)

Source: Clinical data scientist and FDA clinical reviewer.
[1] Coded as Medical Dictionary for Regulatory Activities preferred terms.
[2] The following terms were combined:
Bacterial infection includes: bacterial infection, tonsillitis bacterial
Fungal infection includes fungal infection, vulvovaginal mycotic infection
Herpes virus includes: oral herpes
Infections include: oral herpes, bacterial infection, fungal infection, gastrointestinal infection, gastrointestinal viral infection, influenza like illness, nasopharyngitis, pulpitis dental, rhinitis, tonsillitis, tonsillitis bacterial, vulvovaginal mycotic infection, hordeolum, sepsis, furuncle, otitis externa, viral respiratory tract infection, gastroenteritis, upper respiratory tract infection, bronchitis, ear infection, respiratory tract infection, rhinovirus infection, sinusitis, urinary tract infection
Nasopharyngitis includes: nasopharyngitis, rhinitis
Upper respiratory tract infection includes: influenza like illness, nasopharyngitis, rhinitis, tonsillitis, viral upper respiratory tract infection, upper respiratory tract infection, respiratory tract infection, sinusitis
Viral infection includes: oral herpes, gastrointestinal viral infection, viral upper respiratory tract infection, rhinovirus infection
Abbreviations: ECU, eculizumab, N, number of subjects; n, number of subjects with adverse event; PGC, pegcetacoplan; RCP, randomized control period

Injection Site Reactions

In Study APL2-302, a TEAE of injection site reaction occurred in 44 of 80 (55%) patients (Table 28). During the RCP, a TEAE of injection site reaction occurred more frequently in the pegcetacoplan group than in the eculizumab group (39% versus 5%). This FDA medical query included PTs such as injection site erythema, injection site reaction, injection site swelling, injection site bruising, and injection site pain. None of the injection site reactions was severe or led to treatment discontinuation. Most injection site reactions were grade 1 or grade 2 in severity.

Table 28. All Injection Site Reactions in the Primary Safety Population, APL2-302

Injection Site Reactions[1]	Run-In Period PGC+ECU N=80 n (%)	RCP PGC N=41 n (%)	RCP ECU N=39 n (%)
Injection site reaction	44 (55)	16 (39)	2 (5.1)
Injection site erythema	31 (38.8)	7 (17.1)	0 (0)
Injection site reaction	7 (8.8)	5 (12.2)	0 (0)
Injection site swelling	8 (10)	4 (9.8)	0 (0)
Injection site induration	5 (6.2)	3 (7.3)	0 (0)
Injection site bruising	3 (3.8)	2 (4.9)	0 (0)
Injection site pain	4 (5)	1 (2.4)	0 (0)
Injection site pruritus	11(13.8)	1 (2.4)	0 (0)
Vaccination site reaction	3 (3.8)	1 (2.4)	0 (0)
Administration site swelling	0 (0)	0 (0)	0 (0)
Injection site hemorrhage	0 (0)	0 (0)	0 (0)
Injection site edema	0 (0)	0 (0)	0 (0)

Injection Site Reactions[1]	Run-In Period PGC+ECU N=80 n (%)	RCP PGC N=41 n (%)	RCP ECU N=39 n (%)
Injection site warmth	0 (0)	0 (0)	0 (0)
Administration site discoloration	1 (1.2)	0 (0)	0 (0)
Administration site erythema	1 (1.2)	0 (0)	0 (0)
Administration site pain	1 (1.2)	0 (0)	0 (0)
Application site pain	1 (1.2)	0 (0)	0 (0)
Injection site mass	1 (1.2)	0 (0)	0 (0)
Injection site rash	2 (2.5)	0 (0)	0 (0)
Vaccination site pain	4 (5)	0 (0)	2 (5.1)

Source: Clinical data scientist and FDA clinical reviewer.
[1] Coded as Medical Dictionary for Regulatory Activities preferred terms.
Abbreviations: ECU, eculizumab, N, number of subjects; n, number of subjects with adverse event; PGC, pegcetacoplan; RCP, randomized control period

Hemolysis

Hemolysis is a key characteristic of PNH. Patients are at risk of hemolysis secondary to the disease, and at risk of breakthrough hemolysis while receiving complement inhibitor therapy. In addition, it is important to determine the frequency of hemolysis with transition from C5 inhibitor therapy to pegcetacoplan.

There was one TEAE of hemolysis during the run-in period of Study APL2-302. TEAEs of hemolysis occurred less frequently in the pegcetacoplan group (4 subjects [10%]) than in the eculizumab group (11 subjects [28%]) during the RCP. The onset of hemolysis during the RCP ranged from Day 9 to Day 112 on eculizumab monotherapy. During the RCP, 10 hemolytic events began between Day 2 and Day 29, 1 began between Day 30 and Day 57, 4 began between Day 58 and 85, and the remainder began between Day 86 and Day 113 for patients receiving eculizumab monotherapy.

In addition, abrupt discontinuation of pegcetacoplan treatment may render PNH RBCs unprotected against complement activation, leading to rapid hemolysis with severe anemia. Hemolysis occurring in study subjects after sudden pegcetacoplan withdrawal was observed during the development program. In Study APL2-204, one subject experienced an episode of hemolysis temporally related to nonadherence to dosing per protocol for 8 days. In Study CP0514, an AE of anemia that was attributed to rebound hemolysis was related to a 20-day interruption of pegcetacoplan treatment in the setting of an SAE of alanine aminotransferase (ALT) increased. If a patient with PNH discontinues treatment with pegcetacoplan, the patient should be closely monitored for signs and symptoms of serious IVH. If discontinuation of pegcetacoplan is necessary, alternate therapy should be considered because PNH is life-threatening if untreated. This important information will be transmitted in labeling.

Thrombosis

There were no events of thrombosis during the run-in period or RCP of Study APL2-302.

Hypersensitivity

There were no events of hypersensitivity during the run-in period or RCP of Study APL2-302. Injection site reactions were frequently reported in this trial. None was severe and there were no discontinuations of study drug.

7.6.1.7. Significant Adverse Events

During the run-in period of Study APL-302, there were two TEAEs grade ≥3 in severity. One subject developed sepsis (see Section 7.6.1.3). Additionally, there was one TEAE of leukopenia. During the RCP, the most common grade ≥3 TEAE for patients receiving pegcetacoplan or eculizumab was hemolysis. The most common TEAEs of grade ≥3 in the total population in the run-in period and the RCP are shown in Table 29.

Table 29. Most Common TEAEs of Grade ≥3 in the Safety Population of APL2-302

Adverse Event[1]	Run-in PGC+ECU N=80 n %	RCP PGC N=41 n %	RCP ECU N=39 n (%)
Infection, all[2]	1 (1.2)	1 (2.4)	0 (0)
Gastroenteritis	0 (0)	1 (2.4)	0 (0)
Sepsis	1 (1.2)	0 (0)	0 (0)
Hemolysis[2]	0 (0)	2 (4.9)	3 (7.7)
Anemia[2]	0 (0)	0 (0)	2 (5.1)
Hyperbilirubinemia, jaundice	0 (0)	0 (0)	1 (2.6)
Cholelithiasis	0 (0)	1 (2.4)	0 (0)
Pyrexia	0 (0)	1 (2.4)	1 (2.6)
Dyspnea	0 (0)	1 (2.4)	0 (0)
Atrial fibrillation	0 (0)	1 (2.4)	0 (0)
Fatigue	0 (0)	1 (2.4)	0 (0)
Decreased appetite	0 (0)	0 (0)	1 (2.6)
Thrombocytopenia	0 (0)	1 (2.4)	0 (0)
Leukopenia[2]	1 (1.2)	0 (0)	0 (0)

Source: Clinical data scientist and FDA clinical reviewer.
[1] Coded as FDA medical query
[2] The following terms were combined:
Anemia includes hemolytic anemia, anemia
Hemolysis includes hemolysis, hemolytic anemia
Infection, all includes gastroenteritis, sepsis
Leukopenia includes neutropenia
Abbreviations: ECU, eculizumab; N, number of subjects in group; n, number of subjects with adverse event; PGC, pegcetacoplan; RCP, randomized control period

7.6.1.8. Laboratory Findings, APL2-302

Hematology

In Study APL2-302, the mean CFB in Hb on Day 1 (at the end of the run-in period) was 3.15 g/dL and the mean CFB in platelets was -30.1×10^9 cells/L. Reticulocytes had a mean CFB of -155.1×10^9 cells/L. On Day 1, 26 of 80 patients (32.5%) had a normal Hb level. In total, 3 of 80 (3.8%) patients had a TEAE of thrombocytopenia and 2 of 80 (2.5%) experienced a TEAE of leukopenia, including neutropenia.

At Week 16 of the RCP, erythrocytes had increased in the pegcetacoplan group (mean CFB 0.9×10^{12}/L) compared with the eculizumab group (-0.003×10^{12}/L). Also, hematocrit increased in the pegcetacoplan group (mean CFB 0.09 L/L) compared with the eculizumab group (mean CFB

0.004 L/L). At Week 16, the pegcetacoplan group had a mean CFB in Hb of 2.74 g/dL, compared with 0.01 g/dL in the eculizumab group. In total, 4 of 41 (4.9%) patients in the pegcetacoplan group and 11 of 39 (28.2%) in the eculizumab group experienced hemolysis, which included a PT of hemolytic anemia. A TEAE of thrombocytopenia occurred in 2 of 41 (4.9%) patients in the pegcetacoplan group and in 1 of 39 (2.6%) in the eculizumab group. One patient (2.4%) in the pegcetacoplan group had a TEAE of eosinophilia.

Overall, changes in hematology parameters were consistent with the efficacy findings.

Chemistry

During the run-in period of Study APL2-302, ALT and aspartate aminotransferase (AST) decreased during the run-in period. The mean CFB in ALT at Day 1 was -2.3 U/L and mean CFB in AST was -8.1 U/L. Direct bilirubin and total bilirubin decreased by a mean of -4.92 µmol/L and -29.7 µmol/L, respectively. Erythropoietin showed a mean CFB at Day 1 of -319 IU/L and LDH a mean decrease of -131 U/L. The mean CFB for haptoglobin was 0.24 g/L.

One subject (b) (6) experienced a TEAE of ALT increased during the run-in period, which was graded as mild. The Applicant considered this event to be possibly related to both pegcetacoplan and eculizumab. Additionally, one subject (b) (6) experienced a TEAE of hyperferritinemia of moderate severity. One of eighty subjects (1.2%) experienced a TEAE of hypercalcemia.

During the RCP, at Week 16, ALT had a mean CFB of -4.8 U/L in the pegcetacoplan group and 1.9 U/L in the eculizumab group. AST at Week 16 had a mean CFB of -7.6 U/L in the pegcetacoplan group and 0.8 U/L in the eculizumab group. The mean CFB at Week 16 for bilirubin was -26.7 in the eculizumab group and -0.9 in the eculizumab group. Direct bilirubin normalized at Week 16 in 27 patients (65.9%) in the pegcetacoplan group and in 7 patients in the eculizumab group (17.9%).

The following chemistry laboratory results were reported as TEAEs:

- Subject (b) (6) (eculizumab group): SAE of severe hyperbilirubinemia.
- Subject (b) (6) (eculizumab group): TEAE of mild hyperbilirubinemia.
- Subject (b) (6) (pegcetacoplan group): TEAE of mild bilirubin conjugated increased.
- Subject (b) (6) (pegcetacoplan group): TEAE of mild blood creatinine increased.
- Subject (b) (6) (pegcetacoplan group): TEAE of mild vitamin B12 deficiency.
- Subject (b) (6) (eculizumab group): SAE of severe hyperbilirubinemia. TEAE of moderate hyperbilirubinemia.

Overall, changes in chemistry parameters were consistent with the efficacy findings.

Coagulation

Coagulation events in two patients were recorded as TEAEs during the RCP:

- Subject (b) (6) experienced a TEAE of D-dimer increased.
- Subject (b) (6) experienced an increased international normalized ratio.

There were no other coagulation abnormalities reported as TEAEs in patients during the run-in period or the RCP.

Urinalysis

Three TEAEs were recorded from the urinalysis results:

- Subject (b) (6) (assigned to the eculizumab group) experienced hemoglobinuria during the RCP from Day 29 to Day 85. This event was graded as mild.
- Subject (b) (6) (assigned to the pegcetacoplan group) experienced a TEAE of hematuria that was graded as moderate.
- Subject (b) (6) (assigned to the eculizumab group) experienced hematuria that was graded as mild.

Vital Signs

During the run-in period, three patients reported a TEAE related to vital sign abnormalities. All three TEAEs were pyrexia and graded as mild. No subject had a temperature >38°C at a clinic visit during the TEAE timeframe. There was no TEAE of hypertension during the run-in period.

During the RCP, 2 of 41 (7.3%) patients in the pegcetacoplan group and 3 of 39 (7.7%) in the eculizumab group experienced a TEAE of pyrexia. Two of these TEAEs were considered SAEs, one for Subject (b) (6) (pegcetacoplan group) and one for Subject (b) (6) (eculizumab group). More details on these SAEs can be found in Section 6.3. Three of forty-one subjects (7.3%) in the pegcetacoplan group and 1 of 39 (2.6%) in the eculizumab group experienced a TEAE of systemic hypertension. One subject (2.4%) in the pegcetacoplan group experienced a TEAE of hypotension.

Electrocardiogram

Overall, there were no clinically relevant trends in ECG findings during the run-in period.

No ECG findings were interpreted as abnormal and clinically significant for either treatment group during this study period. Atrial fibrillation was reported as an SAE during the study period in Subject (b) (6), assigned to the pegcetacoplan group, but the rhythm was not recorded (the SAE did not occur at a study visit).

Immunogenicity

Of 316 samples screened for antipegcetacoplan peptide antibody response, 2 (0.6%) were confirmed positive. Subjects (b) (6) and (b) (6), both from the eculizumab monotherapy group, had a confirmed positive result for antipegcetacoplan peptide antibody at Week 16, each with a titer of 1:10. Per the Applicant, the observed positive response to antipegcetacoplan peptide antibody was not associated with safety issues in these two patients.

Anti-PEG antibodies were confirmed in predose samples from 66 of 80 (83%) subjects screened before receiving treatment with pegcetacoplan. The Applicant attributes this high percentage of anti-PEG antibody response to preexisting antibodies from prior pegcetacoplan exposure developed after prior exposure to PEG-containing medicines, cosmetics, or food products.

Of 316 serum samples tested at Week 16, 194 (61.4%) were confirmed positive for anti-PEG antibodies. Only two subjects were categorized as developing a treatment-emergent or treatment-boosted anti-PEG antibody response:

- Subject (b) (6) from the pegcetacoplan monotherapy group developed a treatment-emergent anti-PEG antibody response as demonstrated by a negative anti-PEG antibody predose then a confirmed positive anti-PEG antibody postdose at Week 1 (titer 1:10).
- Subject (b) (6) from the pegcetacoplan monotherapy group developed a treatment-boosted anti-PEG antibody response as demonstrated by a greater than four-fold increase in titer compared to predose. This patient returned to a negative result by the Week-16 ADA sample. This response was considered transient.

In conclusion, the Applicant reports a low incidence of an antipegcetacoplan peptide antibody response (2 of 80 subjects or 2.5%) in this trial. A higher frequency of anti-PEG antibody response was detected in study samples due to preexisting anti-PEG antibodies. The titers associated with an antipegcetacoplan peptide antibody response, treatment-emergent anti-PEG response, and treatment-boosted anti-PEG response were low (<1:40). Due to ADA assay deficiency, the clinical impact cannot be adequately assessed, as stated in the USPI.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Risk of Serious Infection Caused By Encapsulated Bacteria

Issue

The Applicant has highlighted the risk, due to C3 inhibition, of serious infections caused by encapsulated bacteria in patients receiving pegcetacoplan.

Background

The Applicant has proposed a boxed warning and risk evaluation and mitigation strategy language to include serious infections caused by encapsulated bacteria due to the mechanism of action of pegcetacoplan. The multidisciplinary team assessed the safety data provided for pegcetacoplan together with the literature regarding inherited C3 deficiency to determine whether this language is appropriate.

Assessment

The mechanism of action of pegcetacoplan is proximal inhibition of the complement system, which creates an increased risk of serious infections caused by encapsulated bacteria, including *S. pneumoniae, H. influenzae*, and *N. meningitidis*. These associations are based on the review of manifestations of inherited C3 deficiencies, which have shown recurrent and severe infections involving the respiratory system, meninges, and bloodstream by the above-mentioned encapsulated bacteria. These infections are serious, life-threatening, and often require hospitalization and significant medical management (Figueroa and Densen 1991; Risitano et al. 2014). This is in contrast to approved C5 inhibitor therapies, which lead to terminal complement

system inhibition and thereby are associated with a risk of invasive and disseminated *N. meningitidis* infection (Ram et al. 2010). Although no infections were identified in the development program, the total number of patients exposed to pegcetacoplan was only 80. Thus, based on the "rule of three," the upper limit of the 95% confidence interval for the frequency of these infections is 100% X 1/(80/3) or 27% (Jovanovic and Levy 1997).

Conclusion

Upon review of the literature of patients with inherited C3 deficiencies, it was determined that there is an increased risk of serious infections by encapsulated bacteria due to upstream C3 inhibition. Therefore, it was determined that a risk evaluation and mitigation strategy and boxed warning for the risk of serious infections caused by encapsulated bacteria is warranted for pegcetacoplan.

7.7.2. Theoretical Increased Risk of Autoimmune Disease Development With C3 Deficiency

Issue

The literature reports a theoretical increased risk of autoimmune disease development in patients with inherited C3 deficiency due to inhibition of the classical complement pathway.

Background

Autoimmune manifestations have been observed in individuals with deficiencies in proximal components of the classical complement pathway. This risk is based on observations that patients with inherited C3 deficiencies develop autoimmune disorders, including systemic lupus erythematosus. Additionally, deficiencies of C3 have been associated with a high frequency of immune complex manifestations, such as glomerulonephritis. Ricklin et al. (2016) showed that up to 15% of C3-deficient patients present with autoimmune disorders (Sturfelt and Truedsson 2005; Schroder-Braunstein and Kirschfink 2019).

Assessment

To date, there have been no reported events of autoimmunity in patients receiving pegcetacoplan for PNH during the 16-week RCP of Study APL2-302. During the open-label phase of Study APL2-302 there were two SAEs for which an underlying etiology of autoimmune disease cannot be excluded. These SAEs were hypersensitivity pneumonitis and macrophage activation syndrome (MAS) in the setting of breakthrough hemolytic anemia. In both of these events, an infectious etiology was excluded by extensive diagnostic work-up. Details of these SAEs are provided in Section 18.1.8.

MAS is a form of secondary hemophagocytic lymphohistiocytosis caused by an immune imbalance, leading to uninterrupted hyperstimulation of the immune system. Secondary hemophagocytic lymphohistiocytosis is triggered by other conditions, including infections, malignancy, and autoimmune diseases. MAS is a form of secondary hemophagocytic lymphohistiocytosis associated with autoimmune diseases (Lerkvaleekul and Vilaiyuk 2018). Therefore, given the reported increased risk of autoimmune disease in patients with inherited C3

deficiency, an underlying etiology of autoimmune disease resulting in the diagnosis of MAS in this patient cannot be excluded.

Hypersensitivity pneumonitis is an immune-mediated inflammatory interstitial lung disease that can result from exposure to inhaled antigens, potentially leading to fibrosis. There are reported cases of individuals with autoimmune disease and hypersensitivity pneumonitis, suggesting a relationship and prognostic significance (Adegunsoye et al. 2017). Therefore, the development of autoimmunity secondary to pegcetacoplan in the patient who developed hypersensitivity pneumonitis during the open-label phase of Study APL2-302 must be considered.

Given the theoretical potential for development of autoimmunity and upon review of these SAEs in the open-label phase of Study APL2-302, a determination was made that patients receiving pegcetacoplan should be monitored for long-term safety, including development of this potential manifestation.

Conclusion

In conclusion, after review of the literature and reports of patients with inherited C3 deficiency, there is evidence to suggest the potential for the development of autoimmunity in this patient population. Therefore, as it is important for the understanding of the safety of pegcetacoplan, a determination was made to issue a postmarketing requirement to monitor long-term safety, including the development of autoimmune disease, in patients with PNH receiving pegcetacoplan.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Age, sex, race, renal impairment, and hepatic function (as evaluated by total bilirubin, albumin, AST, or ALT) have no clinically significant impact on pegcetacoplan PK. Therefore, no dose adjustment is needed for these intrinsic factors.

Body Weight

Based on a population PK analysis of pegcetacoplan, baseline body weight was a significant PK covariate (Table 30). Compared to a reference 70 kg subject, the weekly average concentration at steady state is predicted to be approximately 14% higher in subjects at the 5th percentile of body weight (54 kg) and 14% lower in subjects at the 95th percentile of body weight (95 kg). Nonetheless, E-R analysis indicates a minimal impact of body weight on the Hb response to pegcetacoplan (Table 31). Therefore, the observed PK changes according to body weight are not clinically significant.

Renal Impairment

Study 205 evaluated the PK of pegcetacoplan following a single dose of 270 mg in subjects with severe renal impairment (CrCl <30 mL/min) compared to matched (sex, age, and weight) healthy subjects with normal renal function. The geometric mean ratio and 90% CI of the C_{max} and AUC for severe renal impairment/healthy controls were 100% (90% CI 76% to 133%) and 92% (90% CI 74% to 112%), respectively. As shown in Table 31, individuals with renal impairment at

baseline are predicted to have a lesser Hb response and steady-state Hb levels are predicted to be 12.8% lower at the 5th percentile of baseline CrCl (50 mL/min) and 12.0% higher at the 95th percentile (221 mL/min) relative to the median baseline CrCl of 120 mL/min. Given that renal impairment does not affect PK, the reduced Hb response with lower CrCl is not likely due to pegcetacoplan exposure, and thus no dose adjustment is needed for patients with mild, moderate, or severe renal impairment.

Other Intrinsic Factors

As shown in Table 30 and Table 31, age, sex, race (Asians versus non-Asians), and liver function—as evaluated by baseline total bilirubin, albumin, AST, and ALT—are not anticipated to have clinically meaningful effects on the pegcetacoplan PK or Hb response.

Table 30. Influence of Covariates on Predicted Pegcetacoplan Steady-State Exposure in Patients With PNH

Covariate	Comparison[1]	Ratio (90% CI) on $C_{avg,ss}$
Baseline weight	54 vs. 70 kg	1.14 (1.11, 1.17)
	95 vs. 70 kg	0.86 (0.83, 0.88)
Age	22 vs. 35 years	1.00 (1.00, 1.00)
	71 vs. 35 years	1.00 (1.00, 1.00)
Baseline albumin	3.6 vs. 4.3 g/dL	0.95 (0.91, 0.98)
	4.9 vs. 4.3 g/dL	1.04 (1.01, 1.07)
Baseline AST	13 vs. 21 IU/L	1.02 (1.00, 1.04)
	116 vs. 21 IU/L	0.94 (0.88, 1.01)
Baseline bilirubin	0.3 vs. 1 mg/dL	1.05 (1.01, 1.09)
	4.3 vs. 1 mg/dL	0.94 (0.90, 0.99)

Source: Report APL-EX20-CP-002 Table 19.
[1] Comparisons for age, weight, albumin, AST, and bilirubin are the 5th and 95th percentiles versus the reference value for subjects in the analysis dataset.
Abbreviations: AST, aspartate aminotransferase; CI, confidence interval; $C_{avg,ss}$, average concentration at steady state; PNH, paroxysmal nocturnal hemoglobinuria

Table 31. Influence of Covariates on Steady-State Hemoglobin Level

Covariate	Comparison[2]	Ratio (90% CI) on Hb
Female sex	Male	0.88 (0.82, 0.94)
Asian race[1]	Non-Asian race	0.94 (0.89, 0.98)
Baseline weight	53 vs. 70 kg	1.06 (1.00, 1.12)
	110 vs. 70 kg	0.92 (0.84, 1.00)
Age	23 vs. 35 years	1.03 (0.99, 1.08)
	72 vs. 35 years	0.96 (0.90, 1.02)
CrCl	50 vs. 120 mL/min	0.87 (0.82, 0.93)
	221 vs. 120 mL/min	1.12 (1.06, 1.20)

Source: Report APL-EX20-CP-003 Table 15.
[1] Includes Japanese ethnicity.
[2] Comparisons for age, weight, and CrCl are the 5th and 95th percentiles versus the medians.
Abbreviations: CI, confidence interval; CrCl, creatinine clearance; Hb, hemoglobin

8.2. Drug Interactions

Pegcetacoplan has a low risk for drug interactions at the intended dose based on the following considerations:

- Pegcetacoplan is a peptide metabolized via catabolic pathways. Therefore, cytochrome P450 (CYP) enzyme inhibitors and inducers are unlikely to affect the PK of pegcetacoplan.
- The in vitro Study 17COTX-001 showed that pegcetacoplan (up to 6 mg/mL) does not inhibit any of the CYP P450 isoforms evaluated (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5) (Study 17COTX-003), either in a direct or metabolism-dependent manner, and does not induce the CYP P450 isoforms evaluated (CYP1A2, CYP2B6, or CYP3A4).
- The in vitro Study 17COTX-002 showed that pegcetacoplan (up to 0.6 mg/mL for uptake transporters and up to 6 mg/mL for efflux transporters) is not a substrate and/or inhibitor for the human drug transporters organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, OATP1B1, OATP1B3, P-glycoprotein (P-gp), or breast cancer resistance protein.

8.3. Plans for Pediatric Drug Development

Orphan Drug designation was granted for this product in April 2014. There was no ongoing or planned pediatric study at the time of application submission.

8.4. Pregnancy and Lactation

The enhanced pre- and post-natal developmental study in monkeys identified a significant increase in abortions and stillbirths at 28 mg/kg pegcetacoplan (2.9-fold the clinical dose based on AUC). The NOAEL for abortions and stillbirths in monkeys was 7 mg/kg/d (NOAEL, 1.3-fold the maximum recommended human dose based on AUC).

Postpartum maternal pegcetacoplan in serum was quantifiable only on postpartum Days 14 and 28 at 7 and 28 mg/kg, respectively. Maternal milk pegcetacoplan concentrations were detectable at 7 and 28 mg/kg up to postpartum Day 14. The pegcetacoplan level in milk was <1% that in plasma. Serum pegcetacoplan levels in infants were not quantifiable on Birth Day 14, 28, 91, or 182.

The cause of increased abortions and stillbirths following exposure to pegcetacoplan is unknown but occurred at a low multiple (2.9-fold) of clinical exposure by AUC, and human risk cannot be discounted. An appropriate description will be included in Section 8 of the labeling.

9. Product Quality

Refer to the reviews by the Office of Product Quality, available in Panorama.

9.1. Device or Combination Product Considerations

Pegcetacoplan is a self-administered BIW as a 1,080 mg SC infusion using a commercially available syringe system infusion pump with a reservoir of at least 20 mL. A patient may self-administer pegcetacoplan with a recommendation to use aseptic technique when preparing and administering the drug. If multi-infusion sets are needed, the recommendation is to ensure that infusion sites are at least 3 inches apart. The typical infusion time is approximately 30 min (if using two infusion sites) or approximately 60 min (if using one infusion site).

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators and Study APL2-302 appears to have been conducted in compliance with United States Regulations pertaining to good clinical practices. Two domestic sites (i.e., #01010 and the Applicant's site) were selected for Office of Scientific Investigations inspections to verify the quality of conduct of the study (Section 21).

11. Advisory Committee Summary

An Advisory Committee meeting was not convened to discuss this application. The study design, endpoints, and statistical plan were acceptable for studies in this indication and the results were clear and noncontroversial. No safety issues were identified that might have benefitted from a public discussion.

III. Additional Analyses and Information

12. Summary of Regulatory History

Investigational New Drug 123087 was submitted on June 13, 2014, to study APL-2 (later called pegcetacoplan) for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). APL-2 is a polyethylene glycol (PEG)-ylated small-molecule inhibitor of complement protein (C) 3 that inhibits C3- and downstream C5-mediated red blood cell (RBC) hemolysis. The protocol entitled *CP0514: An 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 Paroxysmal Nocturnal Hemoglobinuria* was deemed safe to proceed on July 11, 2014.

APL-2 was granted Orphan Drug designation for the treatment of PNH on April 20, 2014.

The Applicant submitted a Fast Track designation request for APL-2 on October 14, 2016, for the treatment of patients with PNH who continue to experience hemolysis and as a result require RBC transfusions despite receiving therapy with eculizumab. Fast Track designation was granted on December 15, 2016.

An additional Fast Track designation request was submitted on December 10, 2018, proposing to broaden the indication of APL-2 for the treatment of all patients with PNH. This Fast Track designation request was granted on February 8, 2019, for the investigation of APL-2 for the treatment of PNH.

Apellis Pharmaceuticals submitted various meeting requests to obtain feedback and guidance in preparation for submission of a marketing application for APL-2. An End-of-Phase 1 meeting was held on November 14, 2017, to discuss the proposed Phase 3 study design to evaluate the safety and efficacy of APL-2 to support an indication for the treatment of PNH.

A Type C meeting was held on March 3, 2017. The purpose of this meeting was to obtain guidance on the overall clinical development program for APL-2, including the design of a Phase 3 clinical study, which would serve as the primary support for a marketing application.

On July 14, 2017, written responses were provided in lieu of a meeting to discuss the Phase 3 protocol, including the primary and key secondary endpoints, inclusion criteria, and proposed statistical analyses for primary and key secondary efficacy endpoints in support of a marketing application.

On August 3, 2017, a meeting was held to discuss the preliminary chemistry, manufacturing, and controls and device data package to support the subsequent New Drug Application (NDA) submission.

A Type B meeting request was submitted on August 10, 2018, to obtain guidance on the Phase 3 program and the proposed design of an additional controlled clinical trial. This meeting request was denied because it was premature to discuss the Phase 3 program at that time.

A pre-NDA meeting was held with the Division on May 20, 2020, during which the Agency was in agreement with the Applicant's plan to submit an NDA on the basis of the Phase 3 clinical trial APL2-302, entitled, *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).*

The Applicant's initial proposed trade name, (b) (4) was found unacceptable on August 13, 2020. A new proprietary name review request was submitted to the NDA with the proposed name of Empaveli, which was found to be conditionally acceptable on December 9, 2020.

13. Pharmacology Toxicology: Additional Information and Assessment

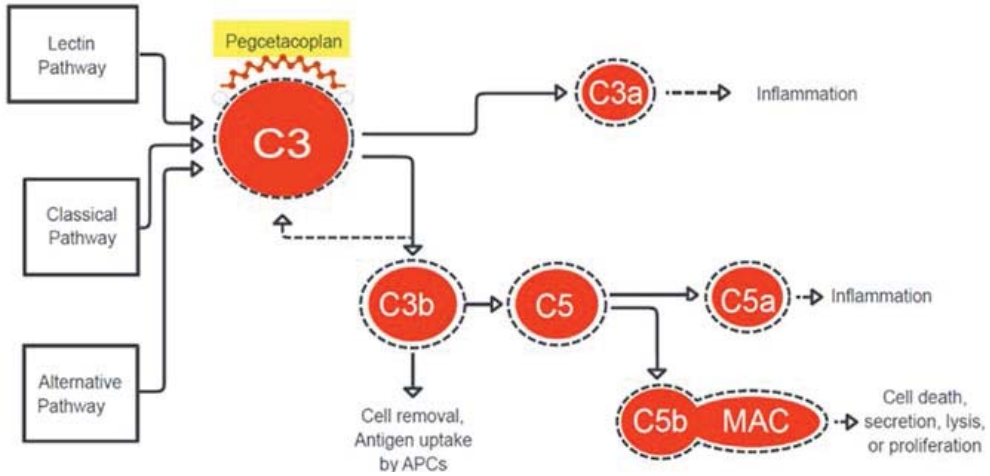
13.1. Summary Review of Studies Submitted Under the IND

Pegcetacoplan Pharmacology

Pegcetacoplan (APL-2) consists of two 15-amino-acid synthetic cyclic peptides (APL-1) covalently bound to a linear 40 kDa PEG (PEG-40) and is indicated for the treatment of PNH.

The active peptide moiety, APl-1, is derived from compstatin, a C3 inhibitor. The PEG-40 component constitutes about (b) (4)% of total pegcetacoplan by weight and prolongs the half-life, making twice a week (BIW) subcutaneous (SC) infusion feasible in humans. Pegcetacoplan selectively binds to C3 and prevents its cleavage to C3a and C3b, thereby reducing the proinflammatory activity of C3a and C3b and preventing formation of the membrane attack complex C5b-9 (MAC).

Figure 17. Pegcetacoplan Mechanism of Action



Source: Apellis Slide, from pre-NDA meeting October 7, 2020.
Abbreviations: APC, antigen-presenting cell; C, complement protein; MAC; membrane attack complex

Pegcetacoplan binds to C3 at nanomolar levels with a binding constant of 15.6nM. Based on binding stoichiometry, one molecule of pegcetacoplan may bind with two C3 molecules, one for each peptide domain in pegcetacoplan (Table 32). It should be noted that pegcetacoplan binds to both C3 and C3b.

Table 32. Pegcetacoplan Binding and Stoichiometry to C3 and C3b

Ligand	C3 K_d, nM	C3, N	C3b K_d, nM	C3b, N
Pegcetacoplan	15.6	0.517	21.3	0.518

Source: Study report 1XTPH-001, Table 1.
Abbreviations: C, complement protein; K_d, binding constant; N, binding stoichiometry

The inhibitory effect of pegcetacoplan on the human classical and alternative complement pathways has been investigated. Pegcetacoplan inhibited both pathways with similar potencies (half-maximal inhibitory concentrations [IC_{50}] of 64 to 136nM) (Table 33). A dose-response curve for the inhibitory activities of pegcetacoplan (APL-2, PEGylated APL-1) and APL-1 (non-PEGylated) on the alternative pathway showed that PEGylation results in a slight leftward shift of the half-maximal effective concentration (EC_{50}) (Figure 2).

Table 33. In Vitro Primary Pharmacology Studies

Study Number and Title	Matrix Type	Concentration	Noteworthy Findings
Study 19CFPH-001 Inhibition of the alternative and classical pathways of complement activation	Serum from: Monkey Sprague–Dawley Rat Rabbit Human	Alternative pathway: 0.002 to 2µM Classical pathway: 9.5 to 10×10^{-6}µM	Pegcetacoplan showed potent inhibition of alternative and classical pathway activation in monkey and human serum. However, a lack of inhibition was observed in rat and rabbit serum. Pegcetacoplan was shown to have inhibitory activity following classical and alternative pathway activation with IC_{50} of 136nM and 64nM, respectively.
Study 18XTPH-001 Isothermal titration calorimetry: C3 and C3b proteins	Pegcetacoplan (Api1514)	20 or 40µM working concentration	Pegcetacoplan (Api1514) was determined to bind both C3 (K_d 15.6nM) and C3b (K_d 21.3nM) proteins with nanomolar affinities.

Source: Derived from studies 19CFPH-001 and 18XTPH-001.
Abbreviations: IC_{50}, half-maximal inhibitory concentration; K_d, binding constant

Ex Vivo and In Vivo Activity

In vivo inhibition of C activation by pegcetacoplan was studied in monkeys. Intravenous (IV) infusion of pegcetacoplan (84 mg/kg) inhibited C3 processing as measured by an increase in the C3 level and a decrease in the C3a level in blood (Figure 4). This inhibitory action on C3 lasted for ≥5 Days and corresponded to elevated plasma pegcetacoplan levels.

Species Specificity

Pegcetacoplan is equally effective in inhibiting C activation by the alternative and classical pathways in both human and monkey serum but exhibited no or minimal activity in serum from mouse, rat, rabbit, or pig (Figure 3).

Safety Pharmacology

Cardiovascular and respiratory safety assessments of pegcetacoplan were conducted in cynomolgus monkeys. Single doses up to 140 mg/kg and a dose of 112 mg/kg PEG-40 did not

result in treatment-related changes in cardiovascular or respiratory parameters in conscious monkeys. Furthermore, pegcetacoplan had no effect on hERG current amplitude in vitro. A dedicated central nervous system safety pharmacology study was not conducted. A tissue distribution study showed that pegcetacoplan was below the level of quantitation following a single dose to monkeys, indicating a minimal risk of acute AEs on the central nervous system.

Pharmacokinetics

The pharmacokinetics (PK) of pegcetacoplan (5% dextrose) was characterized in the nonclinical program primarily in cynomolgus monkeys. Bioavailability is estimated to be about 85% following repeat SC dosing. As expected, PEGylation increased pegcetacoplan steady state half-life to 7.5 hr in monkeys. The clearance (CL) and volume of distribution (V_d) of pegcetacoplan following a single IV infusion were 4.5 mL/kg and 50 mL/kg, respectively. Plasma protein binding of pegcetacoplan has not been determined. Single-dose tissue distribution studies found ^{3}H-pegcetacoplan to be well-distributed throughout the body with the highest concentration present at the SC injection sites followed by blood >lung >kidney >spleen >liver (Table 34). These tissues with ^{3}H-pegcetacoplan were also marked by the presence of cellular vacuolation in the toxicology studies, demonstrating that clearance was taking place in each tissue.

Table 34. Concentrations of Radioactive Material in Principal Tissues of Male Cynomolgus Monkeys After a Single 7 mg/kg SC Dose of ^{3}H-Pegcetacoplan

Tissue	Concentration (ng.equiv/g)				
	8 h	72 h	168 h	336 h	504 h
Blood	3904	4166	2529	1467	787
Adrenal gland	1593	2783	1449	943	264
Bone marrow	912	1510	488	369	173
Brain	BLQ	BLQ	BLQ	BLQ	BLQ
Eye	169	NR	BLQ	BLQ	BLQ
Fat (brown)	938	381	603	518	NR
Fat (white)	BLQ	BLQ	BLQ	BLQ	BLQ
Kidney	2225	3058	1270	938	558
Large intestine	699	1059	621	367	162
Liver	1850	1900	1396	966	552
Lung	2576	2928	1369	1023	606
Myocardium	969	1087	658	680	435
Small intestine	909	1143	605	444	266
Spleen	1799	1270	1136	858	557
SC dose site[a]	494866	10633	BLQ	1114	1599

Source: Apellis, Module 2.6.4, page 11, Study Report 17MTX-001.
[a] One or more samples above the upper limit of quantitation (<349,899 ng-equiv/g).
Abbreviations: BLQ, below limit of quantitation; equiv, equivalent; h, hour; NR, not represented; SC, subcutaneous

Metabolism of the peptide component of pegcetacoplan would follow that of other proteins and was not specifically investigated. Pegcetacoplan neither induced nor inhibited cytochrome P450

(CYP) enzymes (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5) indicating a low potential for metabolic interaction with other drugs. In vitro studies have not shown pegcetacoplan to be a substrate or inhibitor of commonly known drug transporters (i.e., organic anion transporter [OAT]1, organic cation transporter [OCT]2, OATP1B1, OATP1B3, P-gp, or breast cancer resistance protein).

Toxicokinetic Data From Cynomolgus Monkey Toxicity Studies

The time to maximum concentration (T_{max}) in monkeys ranged from 8 to 24 hr. Systemic exposure tended to increase less than dose-proportionally, with no evidence of accumulation. See Table 35.

Table 35. Exposure Multiples for Pegcetacoplan Based on AUC

Study	Dose, mg/kg	AUC_{0-24}, µg.h/mL	NOAEL, mg/kg	Pegcetacoplan Exposure Margin Based on AUC[1]
Six-month rabbit	1	993		<1
	7	69,805		<1
	28	21,500		1.4
Nine-month cynomolgus monkey	1	4035		<1
	7	21,950	7	1.4
	28	45,150		2.9
Monkey enhanced pre- and post-prandial development (GD 48 AUC)	7	20,500	7	1.3
	28	44,300		2.9
Clinical dose, 1,080 mg BIW		~15,506		

Source: Toxicokinetic data from toxicology Study Reports 15CATX-03, 15CATX-004, and 18CATX-001.
[1] The recommended clinical dose of pegcetacoplan is 1,080 mg SC infusion BIW. The AUC_{0-24} at steady state for 1 week was estimated to be 108,541 µg.hr/mL, divided by seven to determine the daily AUC_{24h} pegcetacoplan exposure in humans.
Abbreviations: AUC, area under the concentration-time curve; AUC_{0-24}, area under the concentration-time curve from time 0 to 24 hr; BIW, twice a week; GD, gestation day; NOAEL, no observed adverse effect level; SC, subcutaneous

The ratio of PEG-40 load in rabbits and monkeys relative to clinical dose of 1,080 mg BIW is shown in Table 36. The highest dose evaluated in the 9-month toxicology study in monkeys was 28 mg/kg, which approximates to a monthly PEG-40 load of 768 mg/kg. In comparison, the PEG-40 load at the proposed therapeutic dose of 1,080 mg BIW was 132 mg/kg/month, almost 5.8-fold lower than the maximum exposure evaluated in monkeys.

Table 36. Comparison of Calculated Cumulative Doses of PEG-40 (PEG Load) at the Pegcetacoplan Doses Administered SC to Animals and Humans

Species	Pegcetacoplan Dose (mg/kg/day)	PEG40 Dose (mg/kg/day)[a]	PEG Doses per month	PEG Load (mg/kg/month)	Animal:Human PEG-Load Ratio
Rabbit, monkey	0.25	0.23	30	6.90	0.05
	1	0.92		27.6	0.21
	3	2.75		82.5	0.63
Rabbit, monkey	7	6.41		192	1.45
	28	25.6		768	5.82
	140	128		3840	29.1
Human	1080 mg twice weekly[b]	16.5[c]	8	132	-

[a] Corrected for percentage of the PEG moiety in pegcetacoplan (approximately 91.5%)
[b] The intended therapeutic dose and regimen in PNH patients [c] Assuming human body weight of 60 kg
Source: Apellis Module 2.4, Nonclinical Overview, page 15.
Abbreviations: PEG, polyethylene glycol; PNH, paroxysmal nocturnal hemoglobinuria; SC, subcutaneous

Toxicology Studies

The toxicity of pegcetacoplan was evaluated in New Zealand rabbits for up to 6 months and in cynomolgus monkeys for up to 9 months. An enhanced pre- and post-natal development (ePPND) study was carried out in cynomolgus monkey. Pegcetacoplan inhibits C activation in monkey but not in rabbit or rodents; therefore, the most relevant toxicological characterization was that in monkey. The data derived from rabbits, in particular, can partly inform on the effect of the PEG component of pegcetacoplan.

SC administration of pegcetacoplan and PEG-40 alone in studies ranging from 28 Days (0, 1, 7, 28, or 140 mg/kg, pegcetacoplan and 25.6 to 112 mg/kg PEG-40) to 6 months in rabbit and 9 months in monkey (0, 1, 7, and 28 mg/kg pegcetacoplan and 25.6 to 112 mg/kg PEG-40) consistently resulted in findings of histiocytic infiltrates and macrophage vacuolation in several tissues, most notably the renal tubules and brain choroid plexus, but also the adrenal glands, bone marrow, liver, mandibular lymph node, ovary, and spleen. These findings were observed at a similar incidence and severity in groups administered PEG-40 only, as well as in rabbits, verifying that the PEG component of pegcetacoplan and not the intended pharmacological effect of C inhibition was causative of the histological changes in these tissues. Vacuolation in these tissues except for the choroid plexus appears to be restricted to phagocytic macrophages and is interpreted as a nonadverse adaptation to the PEG moiety of pegcetacoplan. However, the PEG-related changes in two tissues merit particular attention: the kidney, due to the additional presence of renal tubular degeneration, and the brain choroid plexus, due to the presence of vacuolation in the choroid epithelium in addition to the infiltrating histiocytes. Table 37 lists selected histopathology findings from these tissues from the chronic toxicology study in monkey.

Table 37. Selected Histopathology Findings in Kidney and Brain, 9-Month Cynomolgus Monkey Studies

SC Dose	Pegcetacoplan		PEG-40	Pegcetacoplan		PEG-40
(mg/kg/day)	7	28	25.6	7	28	25.6
Finding	**Male**			**Female**		
Kidney tubular degeneration, min	0	2	0	0	4	1
Kidney tubular vacuolation, min	1	5	3	0	5	4
Brain, choroid plexus vac, min to mild	5	0	0	3	0	0
CP epithelial vacuolation, moderate	1	6	6	0	6	6
CP histiocytic infiltration, min to mild	5	0	0	6	0	0
CP histiocytic infiltration, moderate	1	6	6	0	6	6

Source: Derived from toxicology Study Report 15CATX-004.
Abbreviations: CP, choroid plexus; min, minimum, PEG-40, polyethylene glycol 40; SC, subcutaneous, vac, vacuolation

Renal tubular degeneration was of minimal severity and was observed at 28 mg/kg pegcetacoplan in monkeys. The minimal severity of renal tubular degeneration did not change but the incidence increased with chronic dosing from 1 to 9 months. The degeneration did not reverse following a 28-day recovery phase, suggesting that although severity may not progress with time of exposure, the histological change is not readily reversible and is likely to be slow. The cause of renal tubular degeneration is unknown, but it coincides with the presence of tubular vacuolation, which is definitively due to the PEG-40 moiety of pegcetacoplan. Kidney is the primary clearance organ for pegcetacoplan and carries a heavy PEG-40 load as determined by the mass balance study, which may also contribute to the tubular degeneration.

Whether the tubular degeneration is secondary to vacuolation or occurs by another mechanism, the lack of elevation in serum blood urea nitrogen and creatinine suggests that renal function is not notably impaired by this histological change to the tubules despite chronic exposure. The renal tubular degeneration occurred in monkeys at 28 mg/kg, or 2.9-fold the clinical dose based on area under the concentration-time curve (AUC), and ~5.4-fold relative to PEG-40 exposure. The no observed adverse effect level (NOAEL) for renal tubular degeneration was at 7 mg/kg with a 1.4-fold safety margin, supporting the renal safety of clinically relevant exposure to pegcetacoplan.

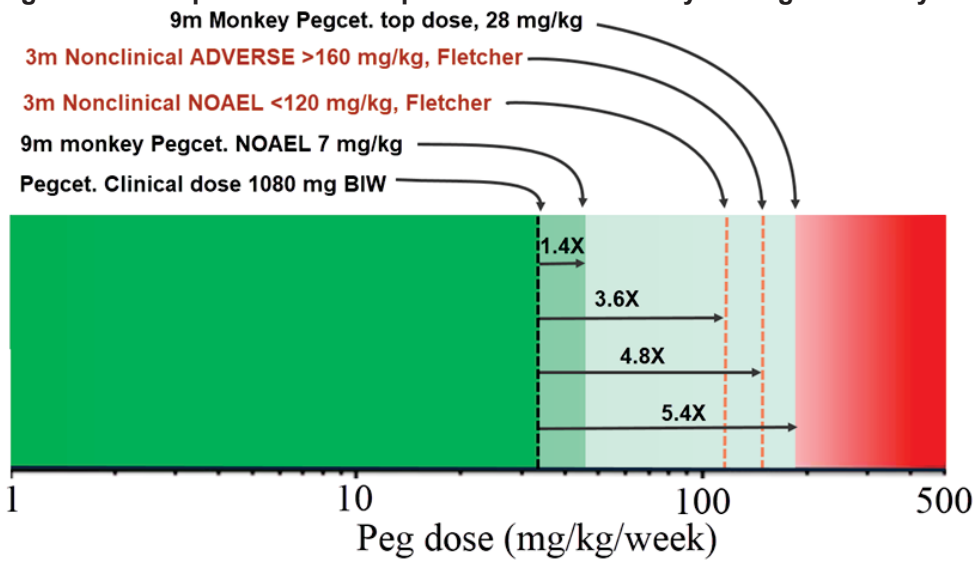
The second toxicological finding of note was minimal to moderate vacuolations of epithelial cells and macrophages in the choroid plexus of monkeys and rabbits. As the finding was observed in both species and with the matching PEG-40 control, this histological change is also definitively linked to the PEG-40 moiety of pegcetacoplan. Vacuolations of choroid plexus and multiple other tissues have been observed with other PEGylated products in animals with the primary concern being whether these vacuolations will eventually result in structural changes that will affect tissue/organ function. Fletcher et al. (2019) reported a study in cynomolgus monkeys administered a PEGylated peptide for a chronic duration (3 months) and provided evidence for a threshold at which accumulation of cellular PEG-40 may become adverse.

Of relevance to the choroid plexus, Fletcher reported sheets of vacuolated macrophages that disrupted the interstitium of the choroid plexus of monkeys at a PEG-40 load of ~160 mg/kg per week, which is appropriately considered an AE on tissue structure. Monkeys administered 7 and 28 mg/kg/d were exposed to a weekly PEG-40 load of ~44 mg/kg and 176 mg/kg for 9 months, respectively, which approximate to 1.4- and 5.4-fold multiples of human exposure to PEG-40 from the clinical dose of pegcetacoplan. Vacuolation of the choroid plexus epithelium was observed at a similar incidence at both doses but with greater severity (to moderate) at the higher 28 mg/kg dose. There was no reported evidence of disrupted tissue structure (e.g., degeneration/

regeneration, necrosis, hyperplasia, interstitial expansion, etc.) of the choroid plexus itself or of the surrounding vasculature and brain tissue at either dose. There was also no adverse clinical signs indicative of neurobehavioral disruption, at least from routine observation in the pivotal toxicology studies.

Although not evaluated in the toxicology studies, pegcetacoplan was below detectable levels in the central nervous system following a single SC administration to monkeys in a tissue distribution study. A more robust evaluation would have included a directed neurobehavioral exam and evaluation of PEG in brain tissue (e.g., histochemistry) and in cerebral spinal fluid from the chronic study in monkeys, particularly at the highest dose administered (28 mg/kg). Nonetheless, at clinically relevant exposure to pegcetacoplan, there is no evidence that vacuolation of the choroid plexus epithelium and attendant histiocytic cells resulted in histological or clinical signs of an AE in the chronic toxicology studies. The fact that the 9-month monkey study with pegcetacoplan did not result in structural changes in the brain choroid plexus similar to those reported by Fletcher et al. (2019) in a 3-month monkey study provides further reassurance of safety. Figure 18 places the clinical exposure to PEG in pegcetacoplan in contrast to exposure in the chronic monkey study and to the PEG-related nonadverse/adverse findings reported by Fletcher et al. (2019). Clinical exposure to pegcetacoplan is concluded to be within an acceptable range of nonadverse exposure to PEG-40.

Figure 18. Multiple of Human Exposure to PEG-40 in Cynomolgus Monkeys



Source: Reviewer's analysis derived from monkey Study Report 15CATX-004 and the published study by Fletcher et al. (2019).
Abbreviations: BIW, twice a week; m, month; NOAEL, no observed adverse effect level; PEG, polyethylene glycol; pegcet, pegcetacoplan

There was no or minimal evidence of antigenicity or evidence of neutralization of pegcetacoplan in cynomolgus monkeys. In comparison, weak to moderate antigenicity of pegcetacoplan was observed in rabbits. As a pharmacologically insensitive species, antigenicity further complicated any signal detected in rabbits.

Carcinogenicity and Genotoxicity Studies

The carcinogenic potential of pegcetacoplan was not investigated in rodents because of the lack of pharmacological activity in species other than humans and monkeys. Suppression of complement activation is not known to be directly associated with carcinogenic signaling

pathways (Hanahan and Weinberg 2011), and no histological findings interpreted as preneoplastic were observed in the toxicology studies conducted in monkeys. Pegcetacoplan is considered nongenotoxic based on results from in vitro and in vivo genotoxicity tests, summarized below.

Study 13BTX-001: In Vitro Bacterial Reverse Mutation Assay on APL-2 and PEG-40

Pegcetacoplan and PEG-40 genotoxicity was evaluated by standard bacterial mutation assay at concentrations up to 5000 µg/plate. There was no evidence of precipitation or toxicity. Neither pegcetacoplan nor PEG-40 was mutagenic in *Salmonella typhimurium* (strains TA98, TA100, TA1535 and TA1537) or *Escherichia coli* strain WPZ uvrA at concentrations up to 5000 µg/plate in the presence or absence of an in vitro metabolic activation system (Aroclor-induced rat-liver S9). The Applicant conducted four Ames tests with newer batches of pegcetacoplan; all results were negative (Study #14BTX-001, 19BTX-001, 19BTX-002, and 19BTX-003).

Study 19BTX-002: Bacterial Reverse Mutation Assay With APL-2 Acetate

Mutagenicity of pegcetacoplan acetate was tested in the standard bacterial strains listed above. Pegcetacoplan acetate was negative for mutagenicity at concentrations up to 5000 µg/plate.

Study 19BTX-003: Bacterial Reverse Mutation Assay With APL-1-AEEAc-Lys-NH2 Trifluoroacetate

Mutagenicity of APL-1-AEEAc-Lys-NH2 trifluoroacetate was tested in standard bacterial strains at concentrations up to 5000 µg/plate. APL-1-AEEAc-Lys-NH2 trifluoroacetate was negative for mutagenicity in the presence and absence of exogenous metabolic activation.

Study 13BTX-002: In Vitro Mammalian Cell Micronucleus Assay in TK6 Cells

Pegcetacoplan at up to 500 µg/mL was subjected to in vitro micronucleus testing using mouse TK6 cells. Pegcetacoplan was non genotoxic when tested at up to 500 µg/mL for 4 hr in an S9-activated system or for up to 27 hr in the absence of S9.

Study 13BTX-003: In Vivo Micronucleus Assay in Mice With PEG-40 and APL-2

Based on a dose range-finding study, pegcetacoplan doses of 500, 1000, and 2000 mg/kg were administered IV to male mice (n=5/group, Study 13BTX-003). Pegcetacoplan was not genotoxic when given by IV injection as two consecutive daily doses of up to 2000 mg/kg.

Summary of Reproductive Studies

Pilot studies assessing potential adverse prenatal developmental effects of pegcetacoplan were conducted in rats and rabbits, which included a PEG-40 control, and in monkeys which did not include a PEG-40 control. There was no evidence of adverse developmental effects in any of these pilot studies. Since rats and rabbits are pharmacologically insensitive to pegcetacoplan, the definitive embryofetal development was addressed in an ePPND study in cynomolgus monkeys. Analysis of placenta and fetuses found detectable levels of pegcetacoplan but at fraction of maternal values, demonstrating that pegcetacoplan can reach placenta and fetuses at a low level (<1% of maternal levels).

Pegcetacoplan was tested at 7 and 28 mg/kg in an ePPND study in cynomolgus monkeys (n=19 to 20/group). Monkeys were injected once daily SC with pegcetacoplan from gestation day (GD) 20/22 until parturition to evaluate the growth and development of infants; the presence of pegcetacoplan in maternal milk while nursing, and neurobehavioral, external, and visceral endpoints in infants. Pegcetacoplan significantly increased the incidences of abortions and stillbirths at 28 mg/kg (2.9-fold the clinical dose based on AUC). The NOAEL for abortions and stillbirths in monkeys was 7 mg/kg/d (1.4-fold the maximum recommended human dose based on AUC).

Maternal pegcetacoplan exposure increased less than dose-proportionally on GD 111 relative to GD 48. After giving birth, maternal pegcetacoplan levels decreased over time and were quantifiable until postpartum day (PPD) 14 and PPD 28 at 7 and 28 mg/kg, respectively. Serum levels in infants were quantifiable on birth day (BD) 14, 28, 91, and 182. Maternal milk pegcetacoplan levels were detectable at 7 and 28 mg/kg up to PPD 14. Pegcetacoplan concentrations in maternal milk were <1% of the plasma levels.

The number of infants per group (9) was consistent with that recommended in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use S6(R1) to allow sufficient evaluation of postnatal development in monkeys.

Impurities and Degradants

Pegcetacoplan has multiple *process* and *degradant* impurities which were qualified by their presence in nonclinical batches (i.e., 140404) used for toxicology studies. (b) (4) is not used in the synthesis of the drug substance but is a potential impurity from its use (b) (4) (b) (4). The Applicant has set the commercial-scale production limit to (b) (4) parts per million. (b) (4) is not genotoxic (negative Ames test) but induces tumors in rodents via a nongenotoxic mechanism (IARC 1987). (b) (4) has modest carcinogenic potency (liver tumors and lymphoma in rodents) with a median toxic dose of (b) (4) mg/kg/day. The calculated threshold of toxicological concern (b) (4) is (b) (4) mg/day (permitted daily exposure level). With (b) (4) levels in the commercial-scale production batches (1000023437 to 1000024996) at < (b) (4) parts per million, the daily human exposure is (b) (4)-fold less than the permitted daily exposure and therefore qualified and acceptable (Table 38).

Table 38. Qualification Levels for Observed Impurities

(b) (4)

Source: Apellis Drug Substance Characterization, Module 2.3.S, Table 10.
Abbreviations: DP, drug product; DS, drug substance; wt%, percentage by weight

13.2. Individual Reviews of Studies Submitted to the NDA

13.2.1. Reproductive and Developmental Toxicology

13.2.1.1. Pilot Prenatal Development

Study 15MTX-001: APL-2: A Pilot Prenatal Developmental Toxicity Study in Rats With a Serum Level Evaluation

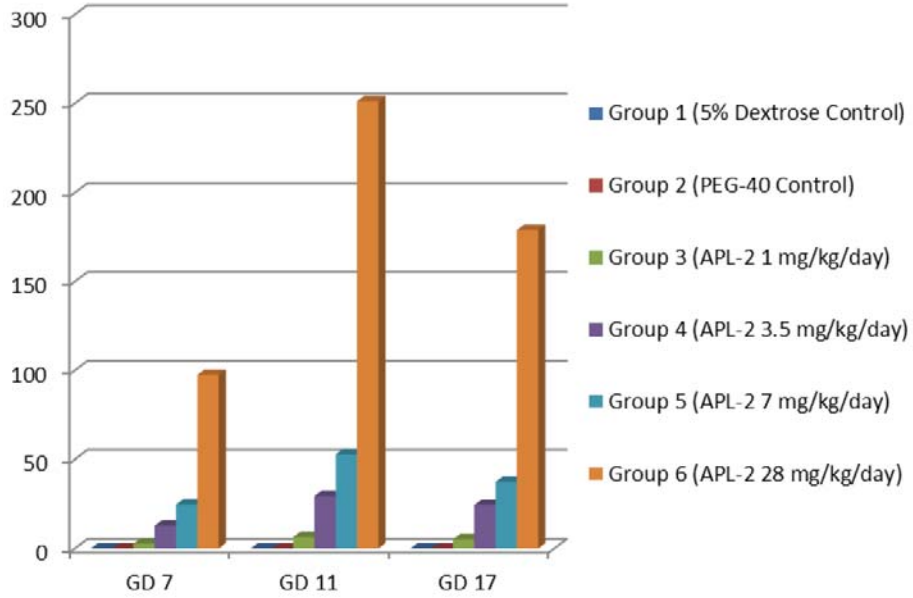
In this prenatal pilot non-good laboratory practices study, pregnant rats (5/group main study, 3/group toxicokinetics [TK]) were treated with 1, 3.5, 7, and 28 mg/kg/day pegcetacoplan from GD 7 to GD 17. The study had two controls, a 5% dextrose diluent vehicle control 1 and a PEG-40 group control 2 (26.2 mg/kg). The study was conducted in 2015.

Findings

There were no pegcetacoplan- or PEG-40–related findings in rats. Neither pegcetacoplan nor PEG-40 affected maternal survival, food consumption, gestation weight, pregnancy rate, uterine implantation, or macroscopic evaluations. There were no pegcetacoplan- or PEG-40–related effects on fetal sex ratio, fetal body weight, or fetal external findings. There were no external malformations or developmental variations among fetuses among groups.

External examination of one fetus from the 28 mg/kg/day pegcetacoplan group revealed a short body, malrotated hind limbs, and filamentous tail. The malformation was within the historical control data and therefore considered spontaneous. Serum pegcetacoplan levels at 28 mg/kg were lower by GD 17 (Figure 19).

Figure 19. Mean Pegcetacoplan Serum Concentration (µg/mL) in Pregnant Rats



Source: Study report 15MTX-001, Figure 1.
Abbreviations: APL-2, pegcetacoplan; GD, gestation day; PEG, polyethylene glycol

Because pegcetacoplan has no notable pharmacological activity in rats, no treatment-related effect is expected. Although the absence of any adverse findings in the PEG control group matching the high-dose pegcetacoplan is reassuring, the study is confounded by the limited number of animals per group.

Study 15MTX-002: APL-2: A Pilot Prenatal Developmental Toxicity Study in New Zealand White Rabbits With a Serum Level Evaluation

This pilot non-good laboratory practices study was designed to evaluate the developmental toxicity/teratogenicity of daily SC administration of 1, 3.5, 7, or 28 mg/kg/day pegcetacoplan from GD 6 to GD 18 in pregnant rabbits (six/group). The study had two controls, a diluent control (5% dextrose) and a PEG control. Satellite rabbits (four mated females/group) were used for TK analysis. The amount of PEG-40 (26.2 mg/kg) in the control group roughly matched the PEG-40 content in the high-dose pegcetacoplan (28 mg/kg) group. Pegcetacoplan is not pharmacologically active in rabbits.

Findings

SC administration of pegcetacoplan at ≥3.5 mg/kg/day and PEG was associated with soft feces. There were no PEG-40– or pegcetacoplan-related finding regarding maternal survival, gestation body weights, gestation body weight change, food consumption, and pregnancy rate. There was no uterine implantation or macroscopic findings in the study. There was no PEG-40– or pegcetacoplan-related change in fetal body weights or evidence of fetal external abnormalities.

Mean serum pegcetacoplan levels appeared to be dose-proportional with no evidence of drug accumulation. The 28 mg/kg pegcetacoplan dose was considered the NOAEL in rabbits.

Study 17CATX-001: A Pilot Embryo-Fetal Development Study of APL-2 by Daily Subcutaneous Injection in Pregnant Cynomolgus Monkeys

This non-good laboratory practices pilot study was designed to address the potential developmental toxicity of pegcetacoplan in cynomolgus monkeys, a pharmacologically responsive animal model (Table 39). The study was conducted in 2017.

The study had only one pegcetacoplan group (28 mg/kg, SC, n=5); 5% dextrose served as the vehicle control (n=3). There was no PEG-40 group to match the PEG-40 content of the highest dose of pegcetacoplan as was the case in the rat and rabbit pilot studies.

Table 39. Study 17CATX-001 Group Information

Group No.	Test Material	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Dose Concentration (mg/mL/day)	No. of Females
1	Diluent (Control Article)	0	1.5	0	3
2	APL-2	28	1.5	18.67	5

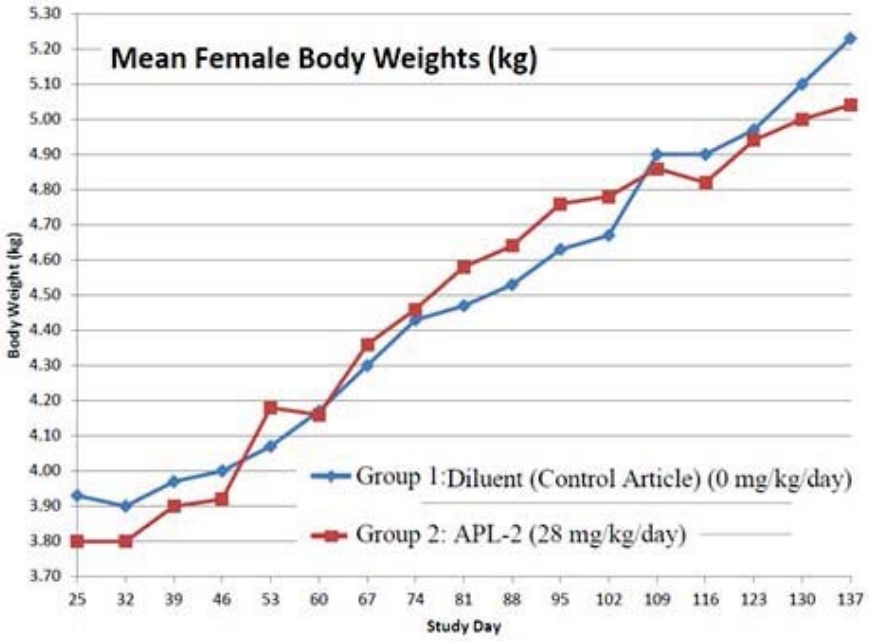
Source: Study Report 17CATX-001, Table 1.
Abbreviations: APL-2, pegcetacoplan; No, number

Animals were dosed SC with 28 mg/kg/day pegcetacoplan from GD 20 to GD 140 (organogenesis, GD 20 to GD 50). Maternal and fetal serum pegcetacoplan levels were measured and fetal viability was assessed by ultrasound measurement of fetal heartbeat. Caesarian section was performed on GD 141. All animals were euthanized at the end of the study.

Findings

Daily SC administration of 28 mg/kg pegcetacoplan from GD 20 to GD 140 (120 doses) to pregnant cynomolgus monkeys produced no effect on survival, maternal body weight (BW), BW gain (Figure 20), food consumption, or pregnancy. There were no pegcetacoplan-related gross findings or organ weight changes, including that of the brain.

Figure 20. Effect of Pegcetacoplan on the Body Weight of Pregnant Cynomolgus Monkeys



Source: Study Report 17CATX-001, Figure 1.
Abbreviation: APL-2, pegcetacoplan

Consistent with the chronic toxicology studies, pegcetacoplan was associated with maternal epithelial and macrophage vacuolation in the brain choroid plexus (Table 40).

Table 40. Effect of Pegcetacoplan on Brain Vacuolation in Pregnant Cynomolgus Monkeys

Summary of Microscopic Findings – Terminal Euthanasia (GD141 ± 1)

Group	2
Dose (mg/kg/day)	28
No. Animals Examined	5
Brain	
Vacuolation, epithelial, choroid plexus	
Mild	5
Vacuolation, macrophage, choroid plexus	
Minimal	1
Mild	3
Moderate	1

Source: Study Report 17CATX-001, Table 11.
Abbreviations: GD, gestation day; No, number

Pegcetacoplan had no effect on embryofetal loss, fetal BW, the placenta, fetal morphometric measurements, teratologic external, visceral, heart, or skeletal evaluations, or other microscopic endpoints. There was no evidence of treatment-related abortions or stillbirths (Table 41).

Table 41. Pregnancy Outcome in Cynomolgus Monkeys Administered Pegcetacoplan

Group No.	No. of Pregnant Females	Dose Level (mg/kg/day)	Mean Gestation Day of C-section	No. of Pregnancy Losses	Number of Fetuses Evaluated
1	3	0	141	0	3 (1 male and 2 females)
2	5	28	141	0	5 (4 males and 1 female)

Source: Study Report 17CATX-001, Table 8.
Abbreviation: No, number

There were no pegcetacoplan-related microscopic findings in the brains of fetuses. Fetal heart rates were comparable between the control and pegcetacoplan dose groups throughout gestation.

Fetal serum samples collected from the umbilicus at 24 hr after the last dose on GD 141 found detectable levels of pegcetacoplan in serum (1.02 to 3.93 µg/mL, mean 2.5 µg/mL). Fetal exposure was a fraction of (0.15%) of the maternal serum pegcetacoplan level (Table 42).

Table 42. Summary of Pegcetacoplan Toxicokinetic Parameters in Pregnant Female Cynomolgus Monkey Serum Following 28 mg/kg SC Administration of Pegcetacoplan on GD 48, 111, and 140

Dose	GD	T_{max}[a] (hr)	C_{max} (µg/mL)	$AUC_{(0-t)}$ (hr*µg/mL)
28	48	8 (8 - 24)	1940 ± 196	45100 ± 4430
	111	8 (0 - 24)	1930 ± 164	44900 ± 3800
	140	8 (0 - 24)	1770 ± 144	40700 ± 3490

[a] Median (Min - Max).
Source: Study Report 17CATX-001, Table 9.
Abbreviations: $AUC_{(0-t)}$, area under the concentration-time curve from time 0 to last measurable concentration; C_{max}, maximum plasma concentration; GD, gestation day; max, maximum, min; minimum; T_{max}, time to maximum concentration

One monkey and its litter tested positive (titer >20) for antidrug antibodies (ADA) with no evidence of ADA or neutralization (Table 43).

Table 43. Summary of Antidrug Antibody Assay Results in Cynomolgus Monkeys

Group	Dose (mg/kg)	No. of Samples		
		Screened Positive	Titer	Specificity Result
1	0	0/15	-	-
2	28	4/32	500-12500[a]	0/4

- Not applicable.
[a] Titer results from Male Fetus No. 2031 (GD141) and Adult Female No. 2503 on GD111 and GD140 (predose).
Source: Study Report 17CATX-001, Table 10.
Abbreviations: GD, gestation day; No, number

Study 18CATX-001: Enhanced Pre-Postnatal Toxicity of APL-2 Administration by Daily Subcutaneous Injection in Pregnant Cynomolgus Monkeys with 6-Month Postnatal Evaluation

Table 44. Enhanced Prenatal and Postnatal Development Study Information

Parameter	Information
Study title	Enhanced Pre- and Post-natal Toxicity of APL-2 Administered by Daily Subcutaneous Injection in Pregnant Cynomolgus Monkeys with 6-Month Postnatal Evaluation
Study number	18CATX-001
Study report location	NDA 000
Date of study initiation	December 20, 2017
GLP compliance	Yes
QA statement	Yes
Drug lot # and % purity	170523W, 97.6%

Source: Derived from Study Report 18CATX-001.
Abbreviations: APL-2, pegcetacoplan; GLP, good laboratory practices; NDA, new drug application; QA, quality assurance

13.2.1.1.1. Key Study Findings

- The study did not have a PEG-40 group as a comparator to pegcetacoplan.
- There were no pegcetacoplan-related findings in monkeys during the gestation and postpartum periods, or in surviving infants up to 180 Days (6 months) postpartum.
- SC administration of 28 mg/kg pegcetacoplan increased the incidence of abortions and stillbirths in monkeys. The exposure at 28 mg/kg was 2.9-fold the estimated human exposure. The cause of the increase in abortions and stillbirths at 28 mg/kg was not determined. The incidences of abortion and stillbirth at 7 mg/kg were similar to the controls and historical background and therefore considered NOAEL for infant mortality (1.3-fold the clinical AUC).
- There was no evidence of ADA in the serum samples tested (all samples were negative).
- Infants of control and pegcetacoplan females generated immunoglobulin M and immunoglobulin G in response to tetanus toxoid immunization. There was no difference in response between the control and pegcetacoplan-treated females.
- Maternal exposure decreased over time and was quantifiable up to PPD 14 and PPD 28 at 7 and 28 mg/kg pegcetacoplan.
- Pegcetacoplan was detected in milk with exposure <1% of maternal plasma levels.
- Pilot embryofetal development study in monkeys with 28 mg/kg pegcetacoplan found quantifiable pegcetacoplan in fetal serum, suggesting pegcetacoplan crosses the monkey placenta and fetal exposure occurs in monkeys at a fraction (0.15%) of maternal serum concentrations.
- With the significant increases in the incidences of abortion and stillbirth, the NOAEL for prenatal maternal or developmental effect was 7 mg/kg pegcetacoplan. The maternal maximum concentration (C_{max}) and AUC at 7 mg/kg on GD 140 was 882 µg/mL and 6890 µg.hr/mL, respectively. The NOAEL for maternal toxicity was 7 mg/kg/d (1.3-fold the clinical dose AUC).

Table 45. Study 18CATX-001 Design

Parameter	Information
Doses	0, 7, and 28 mg/kg
Frequency of dosing	Daily
Dose volume	1.5 mL/kg
Route of administration	Subcutaneous
Formulation/vehicle	5% Dextrose
Species/strain	Cynomolgus monkeys
Number/sex/group	19 to 20 pregnant monkeys per group, no satellite group
Study design	Monkeys were injected daily starting on GD 20 until parturition. Treatment was terminated in the event of an abortion or stillbirth and adults were released. The neurobehavioral assessments of infants were assessed on BD 7 and BD 14 for righting, palmar grasp, clasp-grasp, visual following, prone progression, lip smack orient, oral reflexes (rooting, sucking, snout reflex), eye reflexes (pupil constriction, nystagmus, glabellar tap) more reflex, negative geotaxis and build up. Additional neurological examinations were performed on BD 91 and BD 175. Dose selection was based on toxicity study finding pilot prenatal study at 7 and 28 mg/kg.
Deviation from study protocol	Due to intrauterine fetal death in two animals, a nonrecovery Caesarian section was performed in females 2520 (7 mg/kg) and 3503 (28 mg/kg). Ultrasound found no fetal heartbeat.

Source: Study Report 18CATX-001.
Abbreviations: BD, birth day; GD, gestation day

Table 46. Study 18CATX-001 Group Allocation

Group No.	No. of Pregnant Females	Test Material	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Dose Concentration (mg/mL/day)
1	20	Vehicle	0	1.5	0
2	20	APL-2	7	1.5	4.67
3	20	APL-2	28	1.5	18.67

Source: Study Report 18CATX-001, Table 3.
Abbreviations: APL-2, pegcetacoplan; No, number

Table 47. Terminal Infant and Fetal Procedures

Group No./ Animals	No. of Animals	Scheduled Euthanasia Day	Procedures				Histology	Histopathology
			External Eval.	Visceral Eval. & Necropsy	Tissue Coll.	Organ Wts		
Aborted Fetuses (prior to GD100)			X	-	-	-	-	-
Aborted Fetuses (GD100 or later) and Stillbirths (GD140 or later)			X	X	X	-	X	X
1 Infants (control)	16	BD182 ± 1	X	X	X	X	X	X
2 Infants (7 mg/kg/day)	12		X	X	X	X	-	-
3 Infants (28 mg/kg/day)	8		X	X	X	X	X	X
Unscheduled Infant Necropsy			X	X	X	-	X	X

Adult Female Procedures					
Unscheduled Adult Female Necropsy	Necropsy	Tissue Coll.	Organ Wts	Histology	Histopathology
	X	X	-	X	X

Source: Study Report 18CATX-001, Table 8.
Abbreviations: BD, birth day; Coll, collection; Eval, evaluation; GD, gestation day; No, number; Wts, weights; X, procedure conducted; -, not applicable

Objectives of ePPND studies:

- To assess potential maternal and developmental effects of pegcetacoplan in pregnant cynomolgus monkeys and their offspring when injected SC once daily from GD 2/22 until parturition.
- To evaluate the growth and development of infants for 6 months postnatally after administration of pegcetacoplan to birth mothers during gestation. Postnatal evaluation focused on growth and development of the offspring and tissue histopathology. Infants were evaluated for external skeletal, and behavioral endpoints during the neonatal period and for external and visceral (developmental) endpoints at the time of necropsy.
- To evaluate if pegcetacoplan was present in maternal milk while nursing.
- To evaluate TK, ADA, and developmental immunotoxicology (T-cell–dependent antibody response).

Table 48. Observations and Results of Mother, 18CATX-001

Parameter	Information
Survival of mother (F0)	No apparent treatment-related deaths. However, two adult females were euthanized (unrelated to pegcetacoplan). An adult female (2515) treated with 7 mg/kg pegcetacoplan was euthanized on PPD 1 due to a vaginal tear. Microscopic findings included minimal vacuolated macrophages in adrenal gland, liver sinusoids, adrenocortical hypotrophy/hyperplasia (likely due to stress) and mononuclear cell infiltrates at the injection sited. There were no gross observations in the brain, and no microscopic findings related to pegcetacoplan in the brain sections. No APL-2–related findings were identified at external, visceral (including heart), skeletal, macroscopic, or microscopic evaluations of the infant (male infant 2151), which was found dead on BD 2. A second female (3519) treated with 28 mg/kg was euthanized on GD 131 due complications of parturition (partially delivered fetus in the breech position). Microscopic findings were consistent with HD pegcetacoplan seen in chronic toxicology studies including vacuolated macrophages, histiocytic infiltration, or epithelial vacuolation of various tissues. Minimal to moderate numbers of vacuolated macrophages were observed in the bone marrow, adrenal gland (moderate), parathyroid gland, thyroid gland, liver sinusoids, mandibular and mesenteric lymph node sinuses, ovary, and splenic red pulp. Minimal to mild histiocytic infiltration was observed in the cervix, pituitary gland (pars nervosa), uterus, vagina, and subcutaneous tissue of the administration site. Minimal vacuolation of synovial epithelium was also noted. Mild to moderate infiltrates of vacuolated histiocytes (macrophages) and epithelial cells in the choroid plexus of the brain. The male fetus from this animal had no notable external, visceral, macroscopic or microscopic findings.
Clinical signs	There were no clinical sings related to pegcetacoplan. There was no pegcetacoplan related change in maternal behavior. All females had milk at lactation checks.
Body weight	No change during gestation or postpartum.
Food consumption	No change.
Uterine content	Animals were returned to the colony. Uterine content was not evaluated.
Necropsy observation	Not examined in the surviving animals.
Toxicokinetics	Maternal pegcetacoplan tended to be lower with time suggesting either faster clearance or neutralization of pegcetacoplan. Pegcetacoplan was detected in milk but at less than1% of parent exposure. Pegcetacoplan crosses placenta with exposure less than 1% of maternal levels.
Stability and homogeneity of dose formulations	Concentrations were within ±10% of target.

Source: Study Report 18CATX-001.
Abbreviations: APL-2, pegcetacoplan, GD, gestation day; HD, high dose; PPD, postpartum day

Infants (F1 Generation)

Survival

Infant survival outcomes are listed in Table 49, Table 50, and Table 51.

- There was no apparent treatment-related effect on survival. Five and one of the delivered infants in the 7 mg/kg and 28 mg/kg groups died or were euthanized within 28 Days postpartum. According to the Applicant, the causes were related maternal neglect, trauma, and death unrelated to treatment.

- The total number of fetuses delivered was significantly reduced in the high-dose group. The number of fetuses in the control and 7 and 28 mg/kg pegcetacoplan groups was 19, 17, and 9, respectively. There was a significant increase in the incidence of abortion (31.6%) and stillbirth (21.1%) at 28 mg/kg compared to the control (5% and 0%, respectively). There was no apparent treatment-related finding in the placenta or infant morphometric abnormalities or histopathology findings.
- The overall fetal loss was 1 of 19 (5%) in the control, 2/19 (10.5%) at 7 mg/kg and 10 of 19 (52.6%) at 28 mg/kg pegcetacoplan (10.5%, 10.5%, and 31.6% at the first, second, and third trimesters, respectively).
- The overall fetal loss at 28 mg/kg was substantially greater than the control and historical data from the laboratory (20 to 42.9%; mean 28.8%).
- The overall fetal loss at 7 mg/kg was similar to the control and historical range for the facility (20 to 42.9%; mean 28.8%).
- With significant increase in the incidence of abortion and stillbirth, the NOAEL for a prenatal maternal or developmental effect was 7 mg/kg pegcetacoplan. The maternal C_{max} and AUC at 7 mg/kg on GD 140 was 882 µg/mL and 6890 µg.hr/mL, respectively.

Table 49. Pregnancy and Postpartum Outcomes

Group No. (Dose Level)	No. of Pregnant Females	Mean Gestation Length[b] (Days)	No. of Pregnancy Losses (Fetus M/F/U)[c]	Fetal Losses (Abortion < GD 140; M/F/U)	Fetal Losses (Stillbirth ≥ GD 140; M/F)	No. of Infants Born (M/F)	No. of Infant Losses[d] (M/F)	No. of Maternal Deaths
1 (0 mg/kg/day)	20	160 ± 5	1 (0,0,1)	1 (0,0,1)	0	19 (7,12)	3 (2,1)	0
2 (7 mg/kg/day)	19[a]	160 ± 6	2 (1,1,0)	0	2 (1,1)	17 (9,8)	5 (4,1)	1
3 (28 mg/kg/day)	19[a]	157 ± 9	10 (3,3,4)	6 (2,0,4)	4 (1,3)	9 (5,4)	1 (1,0)	1

U = unable to determine sex; GD = gestation day.

[a] One female from this group was determined not pregnant based on mCG analysis.

[b] Values were calculated including only females that delivered live infants.

[c] Pregnancy losses include abortions (GD20-139) and stillbirths (≥ GD140).

[d] Combined fetal and infant losses were 20.0%, 36.8%, and 57.9% for the control, 7 mg/kg/day, and 28 mg/kg/day groups, respectively, compared to the historical control range of 20.0 to 42.9% for 23 ePPND studies conducted at the Testing Facility from 2008 to 2018.

Source: Study Report 18CATX-001, Table 12.

Abbreviations: ePPND, enhanced pre- and post-natal development; F, female; GD, gestation day; M, male; mCG, monkey chorionic gonadotropin; No, number; U, unable to determine

Table 50. Fetal Losses by Abortion and Stillbirths in Monkeys Treated With Pegcetacoplan

Group No. (Dose Level)	No. Pregnant Enrolled	Adult Female No./Fetus No. (Gestation Day of Fetal Loss)	Overall Percent Loss	1st TM GD20-50[b]	2nd TM GD51-100	3rd TM > GD100[c]
1 (0 mg/kg/day)	20	1510/NA (32)	5.0%	1	0	0
2 (7 mg/kg/day)	19[a]	2517/2171 (156) 2520/2206 (153)	10.5%	0	0	2
3 (28 mg/kg/day)	19[a]	3502/NA (32) 3503/3031 (143) 3510/3101 (124) 3511/NA (73) 3513/3136 (146) 3514/3140 (81) 3515/NA (33) 3516/3166 (158) 3519/3191 (131) 3520/3206 (150)	52.6%	2	2	6
Historical control range for 23 ePPND studies conducted at the Testing Facility from 2008 to 2018.			6.7 to 38.9%	0-15.8%	0 to 10%	0 to 28.6%

GD = gestation day; TM = trimester; NA = not assigned due to gestational age.
[a] One female from this group was determined not pregnant based on mCG analysis.
[b] For abortions in the first trimester, the adult females were confirmed to be pregnant by mCG analysis.
[c] Pregnancy losses from > GD100 include abortions (GD100-139) and stillbirths (≥ GD140).
Source: Study Report 18CATX-001, Table 13.
Abbreviations: ePPND, enhanced pre- and postnatal development; GD, gestation day; mCG, monkey chorionic gonadotropin; NA, not assigned due to gestational age; No, number; TM, trimester

Table 51. Summary of Infant Loss and Mortality

Group No. (Dose Level)	Total No. Infants	Adult Female No./Infant No. (Gestation Day of Delivery)	Birth Day of Loss[a]	Comment
1 (0 mg/kg/day)	19	1503/1036 (162)	1	Infant euthanized; maternal neglect and no cross-foster options.
		1514/1141 (152)	11	Infant euthanized; low fetal heart rate was detected at ultrasound on GD130 (88 bpm) that was labored and weak.
		1509/1091 (154)	11	Infant found dead; maternal induced trauma.
2 (7 mg/kg/day)	17	2505/2051 (165)	2	Infant found dead.
		2510/2101 (152)	10	Infant neglected by the birth mother and found dead after being cross-fostered by Adult Female No. 2505.
		2511/2111 (159)	2	Infant found dead.
		2512/2126 (157)	11	Infant euthanized.
		2515/2151 (157)	2	Birth mother euthanized on PPD1 due to irreparable vaginal tear. The infant was cared for by technical staff but found dead in incubator.
3 (28 mg/kg/day)	9	3506/3061 (144)	2	Infant found dead; maternal induced trauma.

bpm = beats per minute; GD = gestation day; PPD = postpartum day.
[a] Infant losses were 15.8%, 29.4%, and 11.1% for the control, 7, and 28 mg/kg/day groups, respectively, compared to the historical control range of 0 to 20.0% in 23 studies at the Testing Facility from 2008 to 2018.
Source: Study Report 18CATX-001, Table 14.
Abbreviation: No, number

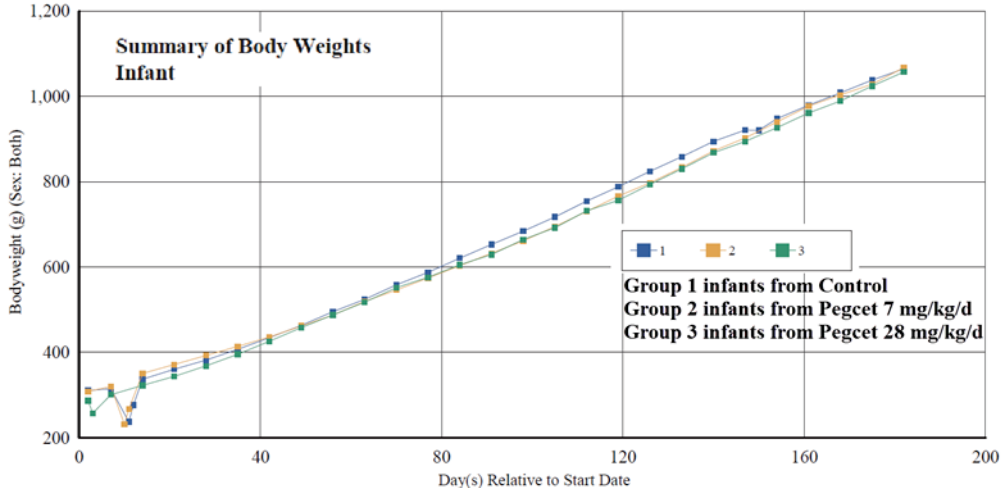
Clinical Signs

- No notable clinical signs were observed in the surviving infants (16, 12, and 8 surviving at 0, 7, and 28 mg/kg, respectively).

Body Weight

- There was no notable change in BW or brain weight.

Figure 21. Summary of Infant Body Weights



Source: Study Report 18CATX-001, Figure 3.
Abbreviation: Pegcet, pegcetacoplan

Food Consumption

- None.

Physical Development

- No treatment-related finding in heart rate or respiration up to BD 180.

Neurological Assessment

- No neurobehavioral (BD 7 and BD 14) or neurological (BD 91/92 and BD 175) findings were observed.

Gross Examination

- No treatment-related change in overall skeletal morphology and maturation.
- No treatment-related fetal or placental findings.
- The internal and external structure of the heart looked normal.

Histopathology

- Infants were euthanized on BD 180 for evaluations. There were no treatment-related findings regarding the external and visceral evaluations, gross pathology, or histopathology. There were no abnormalities in the brain of the infants.
- There were no microscopic findings in the brain of the control or 28 mg/kg pegcetacoplan group.

TK Analysis (Table 52 and Table 53)

- T_{max} averaged about 8 hr, except for 28 mg/kg on GD 48, which had a T_{max} of 24 hr.
- Systemic exposure increased less than dose-proportionally, with no accumulation.
- Maternal serum pegcetacoplan levels decreased with time and were quantifiable only on PPD 14 and 28. Maternal milk levels at 7 and 28 mg/kg decreased or were similar between PPD 7 and PPD 14, suggesting that milk levels were changing as the maternal serum levels decreased.
- No quantifiable pegcetacoplan was detected in the serum of infants at BD 14 and 28 and at necropsy (BD 182).
- Pegcetacoplan levels in serum were substantially greater than the levels in milk on PPD 14 (192 versus 6750 ng/mL), suggesting that milk drug levels were <1% of the serum levels.
- There was no evidence of ADA in the serum samples tested.

Table 52. Pegcetacoplan Toxicokinetic Parameters (Mean±SD) in Pregnant Female Cynomolgus Monkey Serum Following 7 and 28 mg/kg/day Subcutaneous Injection of Pegcetacoplan

Analyte	Gender	GD	Dose (mg/kg/day)	T_{max}[a] (hr)	C_{max} (µg/mL)	$AUC_{(0-t)}$ (hr*µg/mL)	R_{AUC}	R_{Cmax}
APL-2	Female	48	7	8 (0 - 24)	1030 ± 128	24000 ± 2980	NC	NC
			28	24 (0 - 24)	1840 ± 223	42400 ± 5110	NC	NC
		111	7	8 (0 - 24)	896 ± 108	20500 ± 2400	0.859 ± 0.0838	0.871 ± 0.0670
			28	8 (0 - 24)	1930 ± 307	44300 ± 5070	1.04 ± 0.0913	1.04 ± 0.133
		140[b]	7	8 (0 - 8)	882 ± 103	6890 ± 790	NA	0.860 ± 0.0876
			28	8 (0 - 8)	1870 ± 228	14500 ± 1660	NA	1.01 ± 0.0794

GD= Gestation Day; NC = Not calculable; NA = Not applicable. [a] = Median (Min – Max).
[b] = T_{max}, C_{max} and $AUC_{(0-t)}$ were estimated using only one time point (8 hours) after dosing on GD 140.
R_{AUC} = $AUC_{(0-t)}$ on GD 111 or 140/ $AUC_{(0-t)}$ on GD 48. R_{Cmax} = C_{max} on GD 111 or 140/ C_{max} on GD 48.
Source: Study Report 18CATX-001, Table 6, page 2081.
Abbreviations: APL-2, pegcetacoplan; $AUC_{(0-t)}$, area under the concentration-time curve from time 0 to last measurable concentration; C_{max}, maximum plasma concentration; SD, standard deviation; T_{max}, time to maximum concentration

Table 53. Serum and Milk Concentrations of Pegcetacoplan and Their Ratios in Cynomolgus Monkeys Following 7 and 28 mg/kg SC Injection of Pegcetacoplan

		Serum Concentration (ng/mL)	Milk Concentration Left (ng/mL)		Serum/Milk Left (Ratio)	Milk Concentration Right (ng/mL)		Serum/Milk Right (Ratio)
Dose (mg/kg/day)	Adult Female Number	PPD 14	PPD 7	PPD 14	PPD 14	PPD 7	PPD 14	PPD 14
7	2501	120000	326	60.6	1980	419	79.4	1510
	2502	289000	93.9	50.6	5710	86.9	42.8	6750
	2503	-	-	-	-	-	-	-
	2504	149000	313	94.1	1580	393	112	1330
	2505	65300	97.3	48.2	1350	99.9	104	628
	2506	345000	371	108	3190	232	136	2540
	2507	106000	90.1	19.9	5330	91.1	57.0	1860
	2508	155000	144	39.5	3920	59.0	34.3	4520
	2509	176000	152	45.3	3890	152	61.7	2860
	2510	179000	QNS	287	624	461	180	994
	2511	137000	QNS	QNS	NC	QNS	712	192
	2512	88300	QNS	QNS	NC	104	301	293
	2513	93800	140	47.1	1990	164	40.5	2320
	2514	89900	64.5	29.2	3080	63.1	28.0	3210
	2515	-	-	-	-	-	-	-
	2516	318000	1300	226	1410	QNS	263	1210
	2517	-	-	-	-	-	-	-
	2518	126000	179	45.2	2790	144	47.4	2660
	2519	152000	QNS	-	NC	158	57.5	2640
	2520	-	-	-	-	-	-	-

		Serum Concentration (ng/mL)	Milk Concentration Left (ng/mL)		Serum/Milk Left (Ratio)	Milk Concentration Right (ng/mL)		Serum/Milk Right (Ratio)
Dose (mg/kg/day)	Adult Female Number	PPD 14	PPD 7	PPD 14	PPD 14	PPD 7	PPD 14	PPD 14
28	3501	365000	304	133	2740	329	110	3320
	3502	-	-	-	-	-	-	-
	3503	-	-	-	-	-	-	-
	3504	641000	613	223	2880	616	231	2770
	3505	756000	598	344	2200	580	334	2260
	3506	-	-	-	-	-	-	-
	3507	673000	665	195	3450	732	235	2860
	3508	533000	534	227	2350	555	230	2320
	3509	529000	500	367	1440	397	407	1300
	3510	-	-	-	-	-	-	-
	3511	-	-	-	-	-	-	-
	3512	559000	279	179	3120	275	56.1	9960
	3513	494000	512	448	1100	521	499	990
	3514	-	-	-	-	-	-	-
	3515	-	-	-	-	-	-	-
	3516	317000	QNS	179	1770	QNS	197	1610
	3517	524000	168	53.4	9810	149	72.3	7250
	3518	-	-	-	-	-	-	-
	3519	-	-	-	-	-	-	-
	3520	254000	151	196	1300	206	192	1320

Source: Study Report 18CATX-001, Tables 4.2, and 4.3, pages 2111-2112.
Abbreviations: PPD, postpartum day; QNS, quantity not sufficient; SC, subcutaneous; -, no sample

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

In vitro studies were conducted with pegcetacoplan to determine its inhibitory potential towards human hepatic microsomal CYP enzymes, evaluate the induction of CYP enzymes in cultures of human hepatocytes, and to assess its substrate and/or inhibitor potential on a panel of human drug transporters.

Protein Binding

The Applicant did not conduct a plasma protein binding study. The binding of pegcetacoplan to C3 occurs in the systemic circulation when the peptide portion of pegcetacoplan binds C3 and exerts a broad inhibition of the complement cascade. Because the structure of pegcetacoplan is two identical cyclic peptides linked by a linear PEG-40 moiety, the potential for distribution in RBCs is considered low.

Induction of CYP Enzymes by Pegcetacoplan

Table 54. In Vitro Assessments of Pegcetacoplan as an Inducer of CYP Enzymes

Test Article	Pegcetacoplan			Pegcetacoplan				
Concentration	0.6 mg/mL	2 mg/mL	6 mg/mL	0.6 mg/mL	2 mg/mL	6 mg/mL		
Isozyme	Enzyme Activity (% PC[1])			mRNA Content (% Adjusted PC[1])			Conclusion	System
CYP1A2							Not an inducer	Human hepatocytes; mRNA and O-dealkylation
Donor AFJ	-1.06	0.277	0.362	3.56	3.76	5.72		
Donor ZHL	0.693	1.11	1.1	6.73	5.81	5.35		
Donor DVA	0.924	1.44	1.6	1.15	1.14	1.6		
CYP2B6							Not an inducer	Human hepatocytes; mRNA and bupropion-hydroxylation
Donor AFJ	-2.91	-0.454	-0.961	7.1	5.92	6.96		
Donor ZHL	0.916	1.49	7.48	7.24	8.02	7.52		
Donor DVA	0.794	1.48	2.38	2.5	2.94	2.61		
CYP3A4							Not an inducer	Human hepatocytes; mRNA and 6β-hydroxylation
Donor AFJ	1.06	2.15	0.429	11.8	12.3	8.51		
Donor ZHL	1.55	1.48	0.992	25.1[2]	23	17.2		
Donor DVA	4.97	3.49	0.957	10	10.9	7.58		

Source: Clinical pharmacology reviewer's table and Study Report 17COTX-001.
Positive controls are known inducers of the respective CYP isoforms.
[1] The positive controls were 50μM omeprazole for CYP1A2, 1000μM phenobarbital for CYP2B6, and 20μM rifampicin for CYP3A4.
[2] In Donor ZHL, the fold induction over the vehicle control was only 2.98 (<4); therefore, pegcetacoplan was not classified as an inducer even though induction accounted for 25.1% (>20%) of the positive control.
Abbreviations: CYP, cytochrome P450; PC, positive control

Inhibition of CYP Enzymes by Pegcetacoplan

Table 55. In Vitro Assessments of Pegcetacoplan as an Inhibitor of CYPs in Human Liver Microsomes

Isozyme	Enzyme	Inhibitor Positive Control[1]	Activity with Inhibitor	Activity with Pegcetacoplan (0.01 to 6 mg/mL)	Conclusion
CYP1A2	Phenacetin O-deethylase	0.5μM fluvoxamine	21.8%	≥87.7%	Not an inhibitor
CYP2B6	Bupropion hydroxylase	600μM orphenadrine	32.2%	≥85.5%	Not an inhibitor
CYP2C8	Amodiaquine N-deethylase	0.1μM montelukast	20.2%	≥95.9%	Not an inhibitor
CYP2C9	Tolbutamide 4-hydroxylase	3μM sulfaphenazole	34.5%	≥94.6%	Not an inhibitor
CYP2C19	S-Mephenytoin 4′-hydroxylase	20μM nootkatone	26.1%	≥87.3%	Not an inhibitor
CYP2D6	Dextromethorphan O-demethylase	0.3μM quinidine	25.6%	≥87.7%	Not an inhibitor
CYP3A4/5	Midazolam 1′-hydroxylase	0.1μM ketoconazole	18.0%	≥91.7%	Not an inhibitor
CYP3A4/5	Testosterone 6β-hydroxylase	0.2μM ketoconazole	15.4%	≥87.8%	Not an inhibitor

Source: Clinical pharmacology reviewer's table and Study Report 17COTX-003.
[1] Positive controls are known inhibitors of the respective CYP isoforms.
Abbreviation: CYP, cytochrome P450

Table 56. In Vitro Assessments of Pegcetacoplan and NADPH as an Inhibitor of CYPs in Human Liver Microsomes

Isozyme	Enzyme	Inhibitor Positive Control[1]	Activity With Inhibitor and NADPH	Activity With Pegcetacoplan (0.001 to 0.6 mg/mL) and NADPH	Conclusion
CYP1A2	Phenacetin O-deethylase	3μM furafylline	12.1%	75.8-108%[2]	Not an inhibitor
CYP2B6	Bupropion hydroxylase	20μM thiotepa	20%	≥92.2%	Not an inhibitor
CYP2C8	Amodiaquine N-deethylase	40μM gemfibrozil-1-O-β-glucuronide	18%	≥96%	Not an inhibitor
CYP2C9	Tolbutamide 4-hydroxylase	10μM tienilic acid	41.8%	≥95.2%	Not an inhibitor
CYP2C19	S-Mephenytoin 4′-hydroxylase	8μM esomeprazole	37.6%	≥84.7%	Not an inhibitor
CYP2D6	Dextromethorphan O-demethylase	2μM paroxetine	13.8%	≥84.4%	Not an inhibitor
CYP3A4/5	Midazolam 1′-hydroxylase	10μM troleandomycin	28.4%	≥94.5%	Not an inhibitor
CYP3A4/5	Testosterone 6β-hydroxylase	100μM erythromycin	32%	≥96%	Not an inhibitor

Source: Clinical pharmacology reviewer's table and Study Report 17COTX-003.
[1] Positive controls are known inhibitors of the respective CYP isoforms.
[2] Not concentration dependent.
Pegcetacoplan concentrations in the preincubation were 10-fold higher than the concentrations listed.
Abbreviations: CYP, cytochrome P450; NADPH, nicotinamide adenine dinucleotide phosphate

In Vitro Transporter Studies

Table 57. Characterization of Known Substrates in HEK293 Cells Transiently Expressed with Human Uptake Transporters, 17COTX-002

Transporter	Probe Substrate	Fold Uptake Over Vector Control
OAT1	^{14}C-Para-aminohippurate (1μM)	54.2
OAT3	^{3}H-Estrone-3-sulfate 1μM)	3.42[1]
OCT2	^{14}C-Metformin 1μM)	12.8
OATP1B1	^{3}H-Estradiol-17β-D-glucuronide 0.5μM)	17.6
OATP1B3	^{3}H-Cholecystokinin octapeptide 1μM)	32.1

Source: Clinical pharmacology reviewer's table.
[1] The criteria for probe substrate uptake was to be at least four-fold uptake over the vector control; the deviation was not expected to affect overall interpretation of the study findings.
Abbreviations: HEK, human embryonic kidney; OAT, organic anion transporter; OCT, organic cation transporter

Pegcetacoplan was tested as a substrate for OAT1, OAT3, OCT2, OATP1B1, and OATP1B3 (Table 57). After treatment with 60 μg/mL pegcetacoplan, there was no detectable pegcetacoplan in cell lysate. When treated with 600 μg/mL pegcetacoplan, there were sporadic peaks that were below the limit of quantification or <1% of the dose. Trace quantities detected in the vector controls demonstrated 6.08- and 3.06-fold uptake with OCT2 and OATP1B3, respectively; however, the actual quantities were not appreciably above background. Pegcetacoplan was not reduced by 50% in the presence of the inhibitor cyclosporine A for OATP1B3; samples for OCT2 uptake of pegcetacoplan in the presence of quinidine showed poor chromatography and were excluded from calculations. Pegcetacoplan is not considered a substrate for these transporters (Table 58 and Table 59).

Table 58. In Vitro Assessment of Pegcetacoplan as an Inhibitor of Human Transporters Expressed in HEK293 Cells

Transporter	Inhibitor	Activity With Inhibitor	Activity With Pegcetacoplan (600 μg/mL)	Activity With Pegcetacoplan (6000 μg/mL)	Conclusion
OAT1	200μM probenecid	18.3%	94.6%	98.8%	Not an inhibitor
OAT3	200μM probenecid	4.05%	96.1%	130%	Not an inhibitor
OCT2	256μM quinidine	6.83%	132%	140%	Not an inhibitor
OATP1B1	10μM cyclosporine A	2.05%	80.2%	80.1%	Not an inhibitor
OATP1B3	10μM cyclosporine A	10.2%	93.9%	93.6%	Not an inhibitor

Source: Clinical pharmacology reviewer's table and Study Report 17COTX-002.
Abbreviations: HEK, human embryonic kidney; OAT, organic anion transporter; OCT, organic cation transporter

Table 59. Assay Controls for Pegcetacoplan as a Substrate and Inhibitor of P-gp and BCRP, 17COTX-002

Transporter	Substrate	ER in sHBSS	ER in sHBSS and 1% HSA and 1% DMSO	ER in sHBSS and 1% HSA and 2μM Zosuquidar	ER in sHBSS and 1% HSA and 1μM Kol143
P-gp	^{3}H-digoxin 1μM	10.6	12.8	1.24 (2.01% activity)	10.6 (81.1% activity)
BCRP	^{3}H-esterone-3-sulfate (ES3)	5.71 (0.1μM ES3	1.88 (1μM ES3 [1]	1.58 (65.5% activity) (1μM ES3	0.934 (-7.53% activity) (1μM ES3

Source: Clinical pharmacology reviewer's table.
[1] 1.88 is below the acceptance criterion of 4, but the Applicant was still able to confirm activity.
Abbreviations: BCRP, breast cancer resistance protein; DMSO, dimethyl sulfoxide, ER, efflux ratio; ES3, ^{3}H-esterone-3-sulfate; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; HSA, human serum albumin; P-gp, P-glycoprotein; sHBSS, Hank's balanced salt solution with 10mM HEPES

Pegcetacoplan was assessed as a substrate at 60 and 600 µg/mL with or without inhibitors. Of all receiver chamber samples, only one displayed a peak above the lower limit of quantitation (0.100 µg/mL). The lack of efflux precluded calculation of apparent permeability and indicated that pegcetacoplan is not a substrate for the efflux transporters P-gp or breast cancer resistance protein (Table 60).

Table 60. In Vitro Assessment of Pegcetacoplan as an Inhibitor of Efflux Pumps, 17COTX-002

Transporter	Substrate	ER in sHBSS and 1% HSA and 1% DMSO	ER in sHBSS and 1% HSA With PGC (600 µg/mL)	ER in sHBSS and 1% HSA With PGC (6000 µg/mL)
P-gp	1µM ^{3}H-digoxin	12.8	4.70 (31.1% activity)[1]	10.1 (77.1% activity)
BCRP	1µM ^{3}H-esterone-3-sulfate	1.88 (1µM ES3	1.79 (89.9% activity)	2.11 (126% activity)

Source: Clinical pharmacology reviewer's table.
[1] IC_{50} studies necessary.
Abbreviations: BCRP, breast cancer resistance protein; DMSO, dimethyl sulfoxide; ER, efflux ratio; ES3, ^{3}H-esterone-3-sulfate; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; HSA, human serum albumin; IC_{50}, half-maximal inh bitory concentration; PGC, pegcetacoplan; P-gp, P-glycoprotein; sHBSS, Hank's balanced salt solution with 10mM HEPES

Possible inhibition of P-gp was noted (Table 60) where the efflux ratio in sHBSS and 1% HAS with pegcetacoplan was decreased to 4.70 (31.1% activity). Because of this reduction in activity, IC_{50} assays were performed using the test article at concentrations of 20, 60, 200, 600, 2000, 6000, and 20,000 µg/mL. In these IC_{50} assays, efflux activity ranged from 108% at 20 µg/mL to 168% at 20,000 µg/mL. Because efflux activity did not decrease in these IC_{50} studies, no inhibition was detected.

14.2. In Vivo Studies

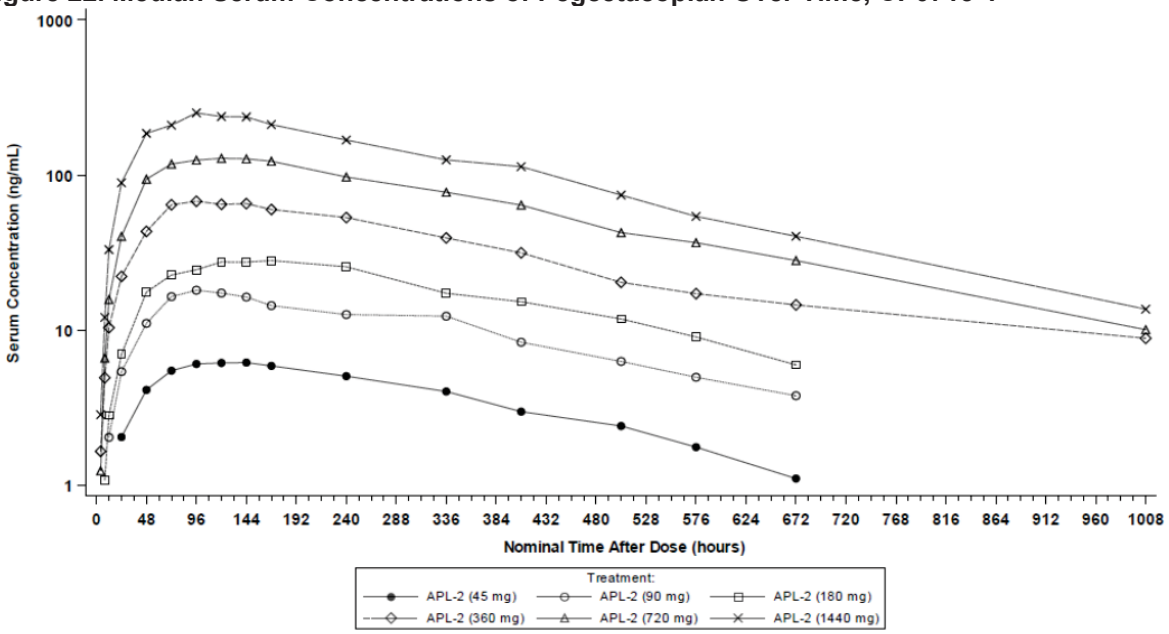
Single Ascending Dose Via SC Administration (Study CP0713-1)

Study Design

This was a randomized, double-blind, placebo-controlled, single ascending dose study to assess the safety, tolerability, PK and pharmacodynamic (PD) characteristics of SC pegcetacoplan in healthy adult subjects. During the study, subjects were randomized to one of six dosing cohorts (45 mg, 90 mg, 180 mg, 360 mg, 720 mg, and 1440 mg). In each cohort, four subjects received pegcetacoplan and two received placebo. Serial PK samples were collected up to 672 hr for Cohorts 1 to 3 and 1,008 hr for Cohorts 4 to 6.

Results

Figure 22. Median Serum Concentrations of Pegcetacoplan Over Time, CP0713-1



Source: Study CP0713-1 Clinical Study Report, Figure 14.2.1.2.
Abbreviation: APL-2, pegcetacoplan

Table 61. Summary of Pharmacokinetic Parameters Following a Single Subcutaneous Dose, CP0713-1

Parameter	Statistics	Pegcetacoplan dose					
		45 mg N = 4	90 mg N = 4	180 mg N = 4	360 mg N = 4	720 mg N = 4	1440 mg N = 4
C_{max} (µg/mL)	Geometric Mean (%CV)	5.8 (34.1)	24.0 (36.4)	31.0 (9.3)	72.0 (26.3)	139 (11.6)	249 (19.6)
T_{max} (h)	Median [Range]	144 [72-168]	108 [96-168]	144 [96-408]	108 [96-144]	132 [96-144]	108 [72-144]
$AUC_{0-\infty}$ (µg·h/mL)	Geometric Mean (%CV)	2611 (28.8)	8096 (18.2)	13,520 (7.4)	28,930 (18.3)	59,040 (12.4)	97,320 (12.6)
$t_{½}$ (h)	Geometric Mean (%CV)	194 (17.9)	223 (18.3)	211 (20.4)	203 (10.1)	235 (6.3)	209 (4.4)
CL/F (mL/h)	Geometric Mean (%CV)	17.2 (28.8)	11.1 (18.2)	13.3 (7.4)	12.4 (18.3)	12.2 (12.4)	14.8 (12.6)
V_z/F (L)	Geometric Mean (%CV)	4.8 (28.2)	3.5 (14.4)	4.04 (13.5)	3.64 (25.6)	4.13 (17.2)	4.45 (9.3)

Source: Study CP0713-1 Clinical Study Report, Table 14.2.1.2.
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve from zero to infinity; CL/F, apparent clearance; C_{max}, maximum concentration; CV, coefficient of variation; N, number; t½, terminal elimination half-life; T_{max}, time to maximum concentration; Vz/F, apparent volume of distribution

Conclusion

Following SC injection, pegcetacoplan T_{max} was 4.5 to 6 days and terminal elimination half-life was 8.1 to 9.8 days across the dose groups. The geometric means for exposure metrics (AUC and C_{max}) increased with dose and were generally proportional from 45 mg to 1440 mg.

Single Ascending Dose Via IV Bolus (Study APL2-401)

Study Design

Study APL2-401 was a double-blind, randomized, placebo-controlled, single ascending dose study of IV pegcetacoplan in healthy subjects. Each subject was randomized to receive a single IV bolus dose of pegcetacoplan administered over a period of approximately 30 min using a syringe pump. There were four dosing cohorts in this study:

- Cohort 1: Single IV bolus of 200 mg pegcetacoplan or matching placebo (4:1).
- Cohort 2: Single IV bolus of 600 mg pegcetacoplan or matching placebo (4:1).
- Cohort 3: Single IV bolus of 1500 mg pegcetacoplan or matching placebo (4:1).
- Cohort 4: Single IV bolus of 2300 mg pegcetacoplan or matching placebo (4:1).

Serial PK, safety, PD, and immunogenic evaluations were performed at specified times throughout the study. The results are listed in Table 62.

Results

Table 62. Summary of PK Parameters Following a Single IV Dose, APL2-401

Parameter	Statistics	Pegcetacoplan dose			
		200 mg (N = 4)	600 mg (N = 4)	1500 mg (N = 4)	2300 mg (N = 3)
C_{max} (µg/mL)	Geometric mean (%CV)	59.88 (26.7)	193.0 (23.3)	562.2 (13.2)	701.0 (17.3)
T_{max} (h)	Median [Range]	1.0 [1-12]	1.0 [0.5-1]	2.5 [0.5-4]	1.0 [1]
AUC_{0-t} (µg·h/mL)	Geometric mean (%CV)	15,480 (28.1)	48,630 (15.2)	112,900 (11.9)	162,500 (14.7)
$AUC_{0-\infty}$ (µg·h/mL)	Geometric mean (%CV)	16,040 (28.4)	51,270 (14.5)	117,000 (12.4)	174,000 (17.7)
$t_{½}$ (h)	Median [Range]	201 [183-234]	222 [217-263]	205 [187-239]	285 [203-302]
CL (L/h)	Geometric mean (%CV)	0.012 (28.4)	0.012 (14.5)	0.013 (12.4)	0.013 (17.7)
V_z (L)	Geometric mean (%CV)	3.7 (30.3)	3.9 (21.0)	3.9 (8.8)	4.9 (13.2)

Source: Study APL2-401 Clinical Study Report, Table 14.2.2.1.2.
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve from zero to infinity; AUC_{0-t}, area under the concentration-time curve from zero to the last measurable concentration; CL, clearance; C_{max}, maximum concentration; CV, coefficient of variation; IV, intravenous; N, number; PK, pharmacokinetic; t½, terminal elimination half-life; T_{max}, time to maximum concentration; Vz, volume of distribution

Conclusion

Following single IV doses of pegcetacoplan from 200 to 2,300 mg, exposure metrics (C_{max} and AUC) increased in a dose-proportional manner. Geometric mean CL values were similar across doses at approximately 0.012 L/h. Geometric mean V_d was similar across dose groups, ranging between 3.7 to 4.9 L. The median $t_{½}$ was long and similar across groups, ranging from 201 to 285 hr (8.4 to 11.9 days), consistent with those calculated after single SC dosing in Study CP0713-1.

Based on cross-study comparison using the dose-normalized AUC from Study CP0713-1 and the current study, pegcetacoplan bioavailability following SC administration is approximately 87%. This estimate is in general agreement with the population PK (PopPK) analysis.

Renal Impairment Study (Study 102)

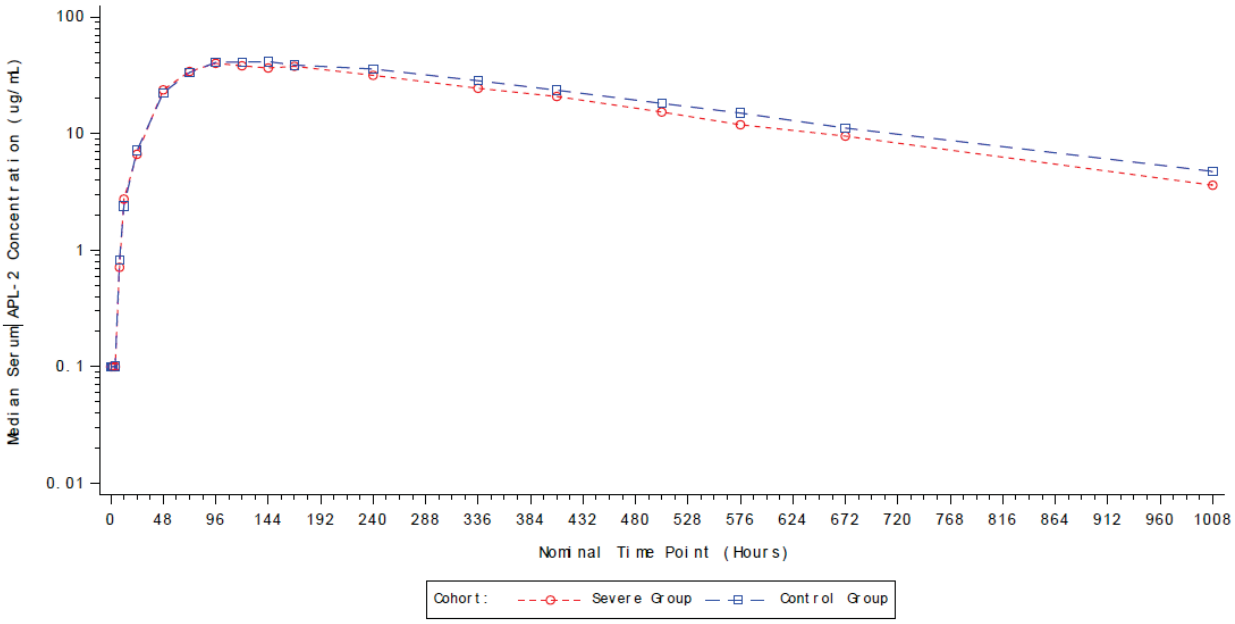
Study Design

This Phase 1, open-label, parallel-group study evaluated the effect of renal impairment on the PK of pegcetacoplan following a single 270 mg SC dose in eight subjects with severe renal impairment (defined as a creatinine clearance [CrCl] <30 mL/min) and eight matched control subjects. PK samples were collected at predose, 1, 2, 4, and 12 hr on Day 1 and on Days 2, 3, 4, 5, 6, 7, 8, 11, 15, 18, 22, 25, 19, and 43. Blood samples for PK assessment were collected on

Day 1 (predose and 1, 2, 4, 8, and 12 hr postdose), and Days 2 to 8, 11, 15, 18, 22, 25, 29, and 43. The results are shown in Figure 23 and Table 63.

Results

Figure 23. Median Serum Concentrations Over Time to Day 43 by Cohort (Log-Linear)



Source: Study 205 Clinical Study Report, Figure 2.
Abbreviation: APL-2, pegcetacoplan

Table 63. Pegcetacoplan Pharmacokinetic Parameters in Subjects With Severe Renal Impairment and Control Subjects With Normal Renal Function

	LS means (back-transformed)		Difference between LS means (90% CI)	Ratio as a percentage (90% CI)
	Control group	Severe group		
C_{max} (µg/mL)	3.67 (39.15)	3.67 (39.27)	0.00 (–0.28,0.28)	100.29 (75.77, 132.75)
$AUC_{0\text{-}inf}$ (h·µg/mL)	9.89 (19,750)	9.80 (18,082)	–0.09 (–0.29,0.12)	91.55 (74.59, 112.37)
$AUC_{0\text{-}t}$ (h·µg/mL)	9.80 (18,037)	9.73 (16,868)	–0.07 (–0.28,0.15)	93.52 (75.27, 116.19)

Source: Study 205 Clinical Study Report, Table 10.
Abbreviations: $AUC_{0\text{-}\infty}$, area under the concentration-time curve from zero to infinity; $AUC_{0\text{-}t}$, area under the concentration-time curve from zero to the last measurable concentration; CI, confidence interval; C_{max}, maximum concentration; LS, least squares

Conclusion

The results indicated that renal impairment does not significantly impact the PK of pegcetacoplan.

PK Comparisons Among Daily, Twice-Weekly, and Once-Weekly Regimens (Study 101)

Study Design

This was a Phase 1, double-blind, randomized, multiple ascending dose study to assess the safety, tolerability, and PK of SC pegcetacoplan in different dose regimens (i.e., daily, BIW, and once weekly) in 40 healthy adult subjects. PK samples were collected before dosing and at 1, 2, 4, 8, 12, and 24 hr after dosing on Day 1 and on Days 3, 4, 5, 6, 8, 15, 22, 23, 24, 25, 26, 27, 28, 29, 35, 42, 56, 70, and 84. On dosing days, samples were collected before dosing.

- Cohort 1: Pegcetacoplan 360 mg daily for 28 days (N=5 with 1 for placebo)
- Cohort 2: Pegcetacoplan 1,300 mg BIW for 28 days (N=5 with 1 for placebo)
- Cohort 3: Pegcetacoplan 2,600 mg once weekly for 28 days (N=6 with 2 for placebo)
- Cohort 4: Pegcetacoplan 1,080 mg BIW for 28 days (N=16, 4/group)
  - Group 1: 30 min infusion alternating between single- and two-needle set (start with a single-needle set)
  - Group 2: 30 min infusion alternating between a single needle and a two-needle set (start with a two-needle set)
  - Group 3: Infusions via a single-needle set, alternating between 1 and 2 hr infusions (starting with a 1 hr infusion)
  - Group 4: infusions via a single-needle set, alternating between 1 and 2 hr infusions (starting with a 2 hr infusion)
- Cohort 5: Pegcetacoplan 1,080 mg BIW for 28 days using a wearable infuser (N=8, 4/group)
  - Small-needle group (inner diameter 0.165 mm)
  - Large-needle group (inner diameter 0.196 mm)

Results

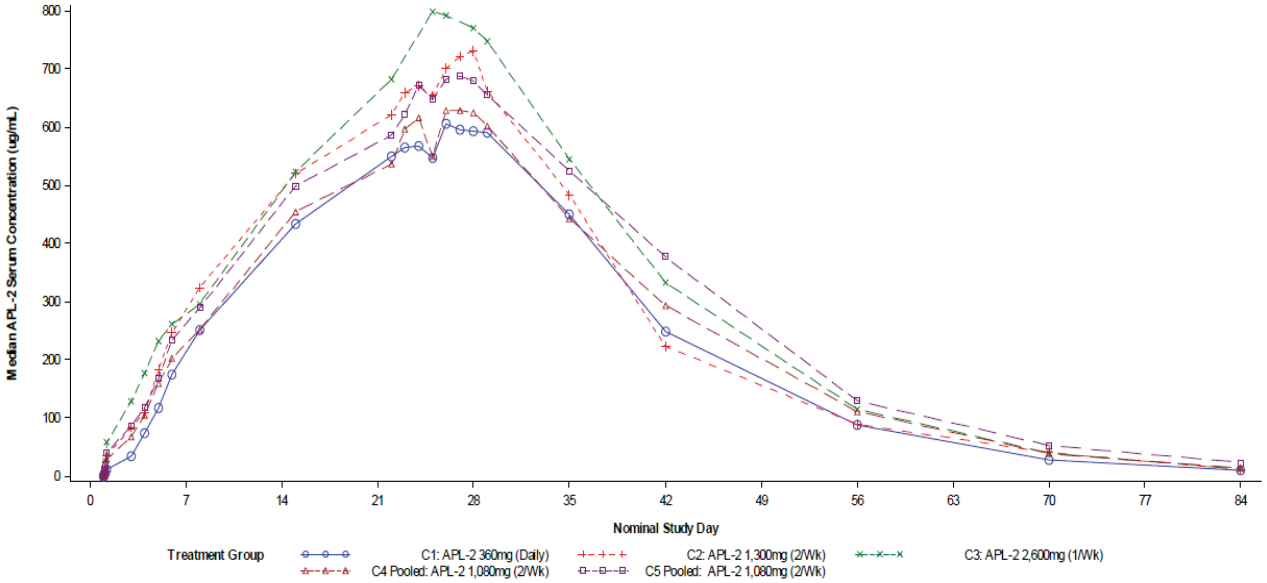
The calculated PK parameters are listed in Table 64 and the mean concentration-time profiles for the full 28-day regimen for each cohort are shown in Figure 24.

Table 64. Summary of PK Parameters Following Multiple SC Doses, 101

Parameter	Statistics	Pegcetacoplan dose				
		Cohort 1 360 mg daily N = 4	Cohort 2 1300 mg 2/wk N = 4	Cohort 3 2600 mg 1/wk N = 3	Cohort 4 1080 mg 2/wk N = 16	Cohort 5 1080 mg 2/wk N = 6
$C_{max, week}$ (µg/mL)	Arithmetic mean (±SD)	628.8 (57.1)	749.3 (69.6)	856.0 (148.2)	685.2 (107.8)	726.0 (44.7)
$C_{min, week}$ (µg/mL)	Arithmetic mean (±SD)	531.5 (52.7)	605.0 (71.5)	658.0 (93.9)	510.3 (66.5)	586.2 (58.4)
T_{max} (h)	Geometric mean (%CV)	641.1 (5.7)	629.7 (3.7)	590.7 (8.3)	618.4 (6.5)	627.2 (5.7)
$t_{½}$ (h)	Geometric mean (%CV)	206.1 (14.2)	221.9 (3.6)	221.9 (12.3)	226.3 (11.2)	243.8 (15.0)

Source: Study 101 Clinical Study Report, Table 14.2.2.1.
Abbreviations: $C_{max\ week}$, maximum concentration over the week; $C_{min,week}$, minimum concentration over the week; CV, coefficient of variation; PK, pharmacokinetic; SC, subcutaneous, SD, standard deviation; t½, terminal elimination half-life; T_{max}, time from the start of dosing on Day 1 to time of maximum observed serum concentration over Days 22 to 29; wk, week

Figure 24. Median Pegcetacoplan Concentration-Time Profiles from Day 1 to 84 by Cohort, 101



Source: Study 101 Clinical Study Report, Figure 3.
Abbreviations: APL-2, pegcetacoplan; C, cohort; wk, week

Conclusion

No large differences in weekly C_{max}, average concentration, or minimum concentration were observed among dosing regimens after means and standard deviations were taken into consideration. This result supports the BIW dosing regimen of 1,080 mg for the pivotal Phase 3 study.

Changes of needle sets (one versus two needle sets), infusion time (30 min to 2 hr) and needle sizes (inner diameter of 0.165 mm to 0.196 mm) had minimal impacts on pegcetacoplan exposure (Table 18 of the Study Report).

14.3. Pharmacometrics Review

14.3.1. Review Summary

The Applicant's PopPK model adequately describes the observed concentrations across the studies in the PopPK analysis for descriptive labeling purposes and for determining individual exposure metrics for exposure-response (E-R) analysis. Parameter estimates for the final model were estimated with acceptable precisions and relative standard errors of <20%. The shrinkages for interindividual variability (IIV) on CL (4.5%), central volume (11%), and absorption rate (13%) were low.

The Applicant's E-R analyses described the relationship between Hb response and time-matched concentrations of pegcetacoplan with a sigmoidal model to estimate maximal proportional change from baseline (CFB) (E_{max}). The estimated E_{max} of Hb was a 36.3% increase from baseline. The pegcetacoplan EC_{50} was estimated to be 272 µg/mL. At the proposed dose (1,080 mg BIW SC), the expected average concentration at steady state of 650 µg/mL is expected to achieve close to the maximal effect for Hb response. Individuals with higher baseline Hb and lower CrCl values are predicted to have a lesser response, in terms of E_{max}. Eculizumab treatment status at baseline is not expected to have meaningful effects on the Hb response.

The E-R relationships for lactate dehydrogenase (LDH) differ between eculizumab-experienced and -naïve patients. This difference is mainly driven by the different baseline LDH levels between these patient groups. Though the magnitudes of E_{max} differed depending on the use of eculizumab at baseline, the EC_{50} estimates are similar between naïve (250 µg/mL) and experienced (173 µg/mL) patients. The proposed dose is expected to provide the maximal effect for LDH control for both the eculizumab-naïve and -experienced patients with PNH.

14.3.2. Population PK Analysis

Applicant's PopPK Analyses

Objectives

- Develop a PopPK model to characterize the concentration-time profiles of pegcetacoplan in healthy adults, adults with renal impairment, and adult patients with PNH.
- Investigate the effects of selected covariates on various pegcetacoplan PK parameters to derive a final predictive PK model.

Data

The PopPK analysis included pegcetacoplan serum concentration-time data from 10 studies: 5 Phase 1 studies in healthy subjects, 1 Phase 1 study in subjects with renal impairment, 2 Phase 1b studies in patients with PNH, 1 Phase 2a study in patients with PNH, and 1 Phase 3 study (data up to Week 16) in patients with PNH (Table 65).

Table 65.Summary of the PK Studies

Study Identifier and Title	Study Population and Number Treated	Regimen and Doses	PK Sampling
Study CP0713-1 A Randomized, Double-Blind, Placebo-Controlled, SAD Study to Assess the Safety, Tolerability, PK and PD of SC APL-2 in Healthy Adult Subjects	Healthy volunteers N=31 (24 pegcetacoplan, 7 placebo)	SAD 45, 90, 180, 360, 720,1440 mg SC ×1	Predose, 1, 4, 8, 12, 24, 48, 72, 96, 120, 144, 168, 240, 336, 408, 504, 576, 672, and 1008 hr postdose
Study CP1014 Phase 1, Double-blind, Randomized, MAD Study in Healthy Volunteers	Healthy volunteers N=20 (16 pegcetacoplan, 4 placebo)	MAD 30, 90, 180, 270 mg SC QD ×4 wks	Predose, 1, 2, 4, 8, 12, and 24 hr postdose on Days 1 and 28 Predose on Days 2, 3, 4, 5, 6, 8, 15, 22, 29, 35, 42, 56, 70, and 84
Study 205 A Phase 1, Single-Dose, Open-Label Study to Evaluate the Effect of RI on the PK of APL-2	Healthy volunteers and RI (8 severe RI, 8 matched controls) N=16 (16 pegcetacoplan)	Single dose 270 mg SC ×1	Predose, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, 168, 240, 336, 408, 504, 576, 672, and 1008 hr postdose
Study 101 Phase 1, Double-Blind, Randomized Study of Daily, Twice-Weekly and Once-Weekly APL-2 in Healthy Volunteers	Healthy volunteers N=40 (36 pegcetacoplan, 4 placebo)	Daily, once weekly, or twice weekly 360 mg SC QD × 4 wks 1300 mg SC twice weekly × 4 wks 2600 mg SC once weekly × 4 wks 1,080 mg SC twice weekly × 4 wks	Predose, 1, 2, 4, 8, and 12 hr postdose on Day 1 Predose on Days 2, 3, 4, 5, 6, 8, 15, 22, 23, 24, 25, 26, 27, 28, 29, 35, 42, 56, 70, and 84
Study APL2-102 Phase 1, Double-blind, Randomized, SAD Study in Healthy Japanese Volunteers	Healthy volunteers N=20 (16 pegcetacoplan, 4 placebo)	SAD 180, 360, 720, 1440 mg SC ×1	Predose, 1, 4, 8, 12, 24, 48, 72, 96, 120, 144, 168, 240, 336, 408, 504, 576, 672, and 1008 hr postdose
Study APL2-401 Phase 1, Double-blind, Randomized, Placebo-controlled, SAD Study of IV APL-2 in Healthy Volunteers	Healthy volunteers N=20 (16 pegcetacoplan; 4 placebo)	SAD 200, 600, 1500, 2300 mg IV ×1	Predose, 0.25, 0.5, 1, 4, 8, and 12 hr postdose on Day 1 Days 2, 3, 4, 5, 6, 7, 8, 15, 22, 29, and 43

Study Identifier and Title	Study Population and Number Treated	Regimen and Doses	PK Sampling
Study CP0514 An Open-Label, Single and Multiple Ascending Dose Study to Assess the Safety, Tolerability, PK and PD of APL-2 as an Add-On to SoC in Subjects with PNH	PNH (eculizumab-treated for ≥3 months) subjects N=15 (12[1] pegcetacoplan)	SAD and MAD Cohort 1: 25 mg SC ×1 followed by 28 Days washout then 5 mg SC QD ×4 wks Cohort 2: 50 mg SC x1 followed by 28 Days washout then 30 mg SC QD × 4 wks Cohort 3: 180 mg SC QD × 4 wks Cohort 4: Daily SC doses of 270 mg for up to 729 Days with optional intrasubject escalation up to 360 to 440 mg/day after Day 28	Cohort 1 and 2: Predose and 4 hr postdose on Day 1; predose on Days 2, 3, 4, 8, 15, 22, 29, 43, 57, 71, 85, 113, and 141 Cohort3: Predose and 4 hr postdose on Day 1; predose on Days 2, 3, 4, 8, 15, 22, 29, 43, 57, 71, 85, and 113 Cohort 4: Predose and 4 hr postdose on Day 1; predose on Days 2, 3, 4, 8, 15, 22, 29, 43, 57, 71, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 421, 477, 533, 617, 729, and 785
Study APL2-204 A Phase 1b, Open-Label, MAD, Pilot Study to Assess the Safety, Preliminary Efficacy, and PK of SC APL-2 in Subjects with PNH. (PADDOCK)	PNH (eculizumab-naïve) subjects N=23 (23[2] pegcetacoplan)	Cohort 1: 180 mg SC QD × 4 wks Cohort 2: Daily SC doses of 270 mg for up to 414 Days with optional intrasubject escalation up to 360 mg/day	Predose and 2.5 hr postdose on Day 1 Predose on Days 2, 3, 8, 22, 29, 43, 71, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 379, 393, and 414
Study APL2-202 A Phase 2a, Open Label, Multiple Dose Study to Assess the Safety, Efficacy and PK of SC APL-2 in Subjects with PNH	PNH (eculizumab-naïve) subjects N=4	Daily 270 mg SC QD ×4 wks, may increase up to 360 mg SC QD × up to 1 year	Predose and 2.5 hr postdose on Day 1 Predose (where applicable) on Days 2, 3, 8, 22, 29, 43, 71, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 379, 393, and 414
Study APL2-302 A Phase 3, Randomized, Multicenter, Open-Label, Active-Comparator Controlled Study to Evaluate the Efficacy and Safety of APL-2 in Patients with PNH	PNH (eculizumab-treated) subjects N=80 (41 pegcetacoplan; 39 eculizumab)	Twice weekly 1,080 mg SC twice weekly or every 3 Days ×1 year	Predose (where applicable) on Days -28, -21, -14, 1, 14, 28, 42, 56, 84, and 112 Additional 6 hr postdose sample on Days 1, 28, and 112

Source: Adapted from the Applicant's PopPK report, Table 1, pages 25 to 29.
[1] Represents nine unique subjects due to re-enrollment of two subjects in multiple study groups.
[2] Represents 22 unique subjects due to re-enrollment of 1 subject in multiple study groups.
Abbreviations: APL-2, pegcetacoplan; IV, intravenous; MAD, multiple ascending dose; PD, pharmacodynamic; PNH, paroxysmal nocturnal hemoglobinuria; PK, pharmacokinetic; PopPK, population pharmacokinetic; QD, once daily; RI, renal impairment; SAD, single ascending dose; SC, subcutaneous; SoC, standard of care; wks, weeks

The final analysis dataset included a total of 239 unique subjects with a total of 4377 PK samples, including 3734 quantifiable samples. Among them, 236 pre–first-dose samples and 407 samples postdose were below the limit of quantification.

For the summary statistics of the baseline demographic covariates in the analysis dataset, refer to Table 5 and Table 6 of the Applicant's PopPK report, page 42. A total of 48.1% of subjects in the dataset was adults with PNH, and 56.5% of patients were male subjects. The majority of subjects (64.4%) was white and 22.2% were Asian (including Japanese) ethnicity. The median age was 35 years (range 19 to 81 years) and median baseline body weight was 71.2 kg (range 42.3 to 156 kg). Median CrCl was 119 mL/min (range 14.6 to 367 mL/min), including the data from a Phase 1 study (Study 205) in a population with renal impairment. Among patients with PNH, the median (range) CrCl was 116 mL/min (30 to 367 mL/min). Based on estimated glomerular filtration rate (eGFR), 15 (6.3%) subjects had moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m^2) and 8 (3.3%) had severe or end-stage renal impairment (eGFR <30 mL/min/1.73 m^2). Subjects with moderate renal impairment were patients with PNH and those with severe renal impairment were included in the population enrolled in Study 205.

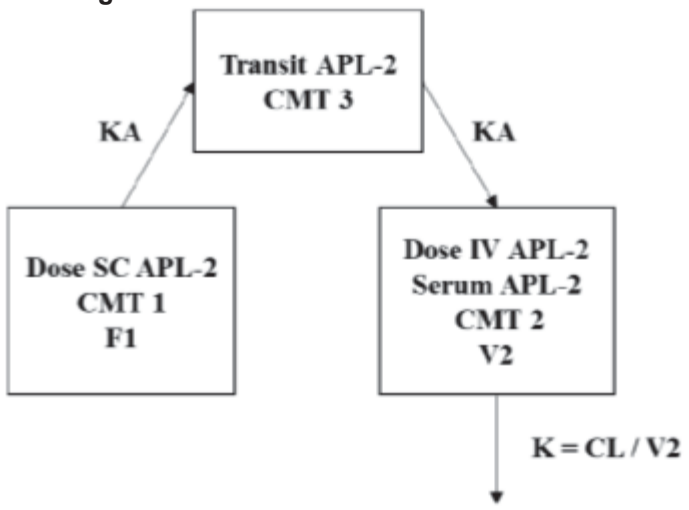
Software

Analyses were performed using the nonlinear mixed effects modeling methodology as implemented in NONMEM® (version 7.3). Data pre- and post-processing, including graphical analysis of the data or output from the models, were performed using R (version 3.6.3).

Base Model

The final base model was a one-compartment disposition, one-transit absorption compartment for SC administration, IV dose administration directly into the central compartment, and first order elimination. The PK were linear over the range of SC single doses studied (45 mg to 1440 mg). The base model included the following structural covariates: (b) (4) formulation on SC bioavailability, C3 level on CL and apparent volume (V2), and PNH patient status divided into Phase 1 or 2 and Phase 3 studies on CL. IIV random effects were included on absorption rate, CL, and V2 with residual error described using a log-additive structure (Figure 25).

Figure 25. Diagram of the Model Structure



Source: Figure 7, Applicant's PopPK report, page 56.
Abbreviations: APL-2, pegcetacoplan; CL, clearance; F1, subcutaneous bioavailability; IV, intravenous, KA, apparent first-order absorption rate constant; PopPK, population pharmacodynamic; SC, subcutaneous, V2, apparent volume

Covariate Analysis

The following nonstructural covariates were included in the covariate full model: body weight, bilirubin, albumin, and aspartate aminotransferase (AST) on CL; weight, age, and baseline eculizumab on V2; PNH patient status, body-mass index, dextrose formulation, and mannitol formulation on absorption rate; and dextrose formulation and mannitol formulation on SC bioavailability. The stepwise backward elimination procedure based on the likelihood-ratio test was used to identify the PK final model. At each step, the covariate-parameter relationship which had the lowest change in objective function value and did not meet the inclusion criteria (change in objective function value >10.8 [p<0.001]) was eliminated and the stepwise backward elimination procedure was repeated until all covariate-parameters met the inclusion criteria. The preliminary final model after backward elimination included only two more covariates than the base model: body weight on CL and V2.

Final Model

The final model consisted of one central disposition compartment, transit compartment absorption (n=1) for the SC route, direct administration into the central compartment for the IV route, and first-order elimination from the central compartment. Covariates included in the final model were the (b) (4) formulation on SC bioavailability; time-varying C3, baseline body weight, and PNH patient status on CL; and time-varying C3, and baseline body weight on V2. The parameter estimates for the final covariate model are listed in Table 66. For a visual predictive check (VPC) plot for the final covariate model with all data, refer to the Applicant's PopPK report, Figure 10, pages 77 to 79. The goodness-of-fit (GOF) plots for the final covariate model for all data are shown in Figure 26.

Table 66. Parameter Estimates for the Final Model

Theta / Parameter (Units)	Final 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 (b) (4) Formulation on F1	0.236	0.0388	16.5	(0.160, 0.312)
9 C3 on CL	-0.122	0.0135	11.0	(-0.149, -0.0957)
10 C3 on V2	-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			

Source: Table 16, Applicant's PopPK report, page 71.
Abbreviations: ASE, asymptotic standard error; CI, confidence interval; CL, clearance; CV, coefficient of variation; ETA, estimate of interindividual variability; F1, subcutaneous bioavailability; IIV, interindividual variability, KA, apparent first-order absorption rate constant; PNH, paroxysmal nocturnal hemoglobinuria; PopPK, population pharmacodynamic; RE, residual error; RSE, relative standard error; V2, apparent volume; WT, weight

Applicant's Conclusions

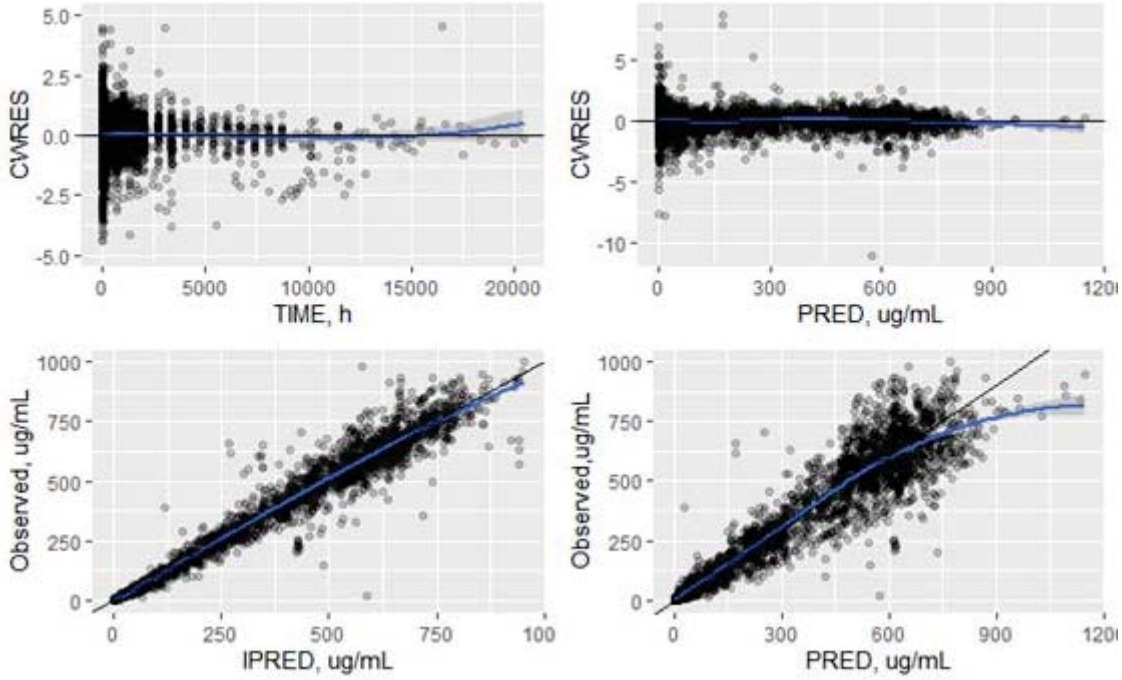
- SC bioavailability was estimated as 76.6% for liquid formulations; higher bioavailability was estimated for the [redacted] (b) (4) formulation (94.7%).
- Patients with PNH are predicted to have lower pegcetacoplan exposure than healthy subjects due to increased systemic CL without a meaningful difference in V_d. The effective half-life of pegcetacoplan at a SC dose of 1,080 mg BIW was estimated as 8 days for adult patients with PNH compared to 10.1 days for healthy adults.
- C3 level had a time-varying impact on both pegcetacoplan CL and V_d. Relative to the median C3 level over time, steady state pegcetacoplan exposure (C_{max} at steady state and average concentration at steady state) was approximately 6% lower at the 5th percentile of C3 level over time and approximately 4% higher at the 95th percentile of C3 level over time.
- Baseline body weight was a significant covariate of both pegcetacoplan CL and V_d. Compared to a reference 70 kg subject, steady-state weekly C_{max} and average concentration at steady state were predicted to be approximately 15% higher in subjects at the 5th percentile of body weight (54 kg) and 15% lower in subjects at the 95th percentile of body weight (95 kg).
- Age, sex, Asian race, Japanese ethnicity, baseline CrCl, baseline total bilirubin, baseline albumin, baseline AST, baseline alanine aminotransferase (ALT), and eculizumab coadministration had no statistically significant impact on the PK parameters of pegcetacoplan.

Reviewer's Assessment of the PopPK Analyses

The Applicant's PopPK model adequately describes the concentrations observed across different studies included in PopPK analysis for descriptive labeling purposes and for determining individual exposure metrics for E-R analysis:

- Parameter estimates for the final model were estimated with acceptable precisions with relative standard error less than 20%. The shrinkage for IIV on CL (4.5%), central volume (11%), and absorption rate (13%) were low. The standard GOF plots (Figure 26) did not show obvious bias on predicted concentrations over time and the individual predicted concentrations and predicted concentrations were in good agreement with the observed concentrations for all studies included in the PK analysis. The GOF plots were further examined by stratifying by study, which revealed no obvious misspecification. The VPCs presented by study demonstrated generally an agreement between the observed and simulated concentrations, except for Study APL2-202, which showed a tendency of underprediction based on data from four patients. In general, the central tendency and variability were adequately captured in Phase 2 and 3 studies in which trough concentrations were measured.

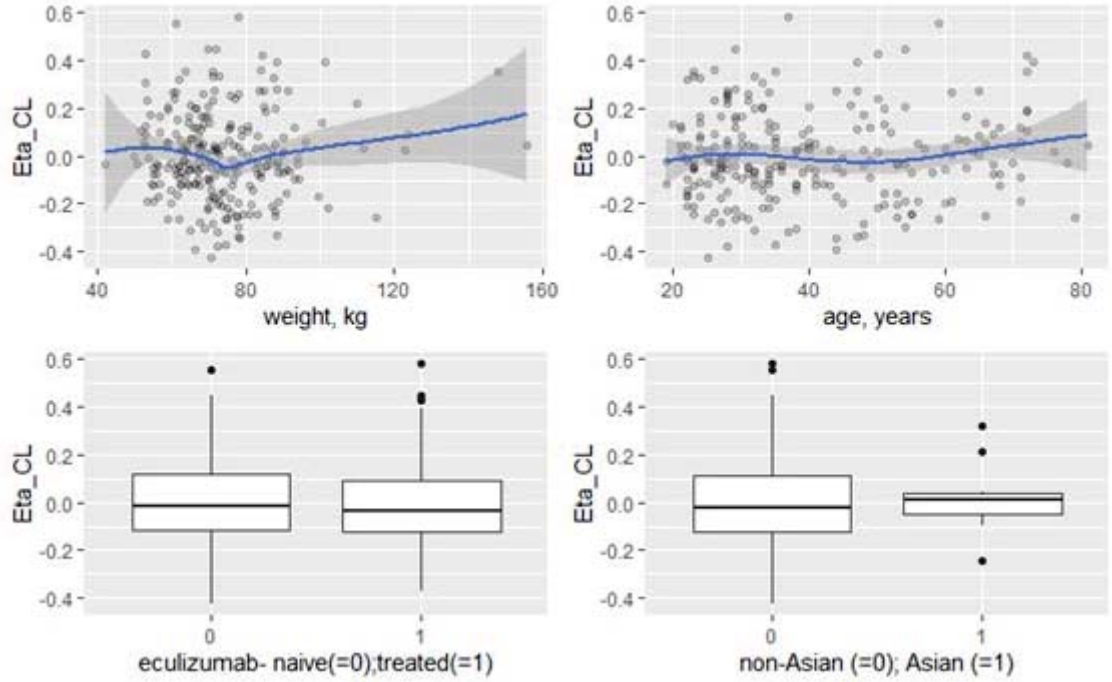
Figure 26. Standard GOF Plots for the Applicant's Final PK Model



Source: Reviewer's plot based on the Applicant's final PopPK model.
Abbreviations: CWRES, conditioned weight residuals; GOF, goodness-of-fit; IPRED, individual predicted concentrations; PRED, predicted concentrations

- Transit compartment incorporated in the final model reasonably captured the slow absorption following SC administration (versus IV).
- The Applicant's final covariate models are adequate. The reviewer examined the relationships between estimates of interindividual variability and the covariates (body weight, age, ethnicity, eculizumab treatment at baseline, AST, ALT, bilirubin, total albumin, and eGFR) and did not note any trends in estimate of interindividual variability (ETA) for CL and V distributions based on the covariates. Only selective relationships for ETA for CL are presented in Figure 27.
  - Body weight effect on apparent CL was estimated as 0.536 (exponent of allometric scaling). There was no bias in ETA on CL over the observed body weight range (Figure 27, top left). The lower estimated scalar suggests that smaller variability in exposure is expected across body weight at the fixed dose (1,080 mg BIW). Dose adjustment based on body weight is not needed.
  - There was no bias noted in ETA of CL based on eculizumab use at baseline (Figure 27, bottom left).
  - The effect of antipegcetacoplan antibodies on pegcetacoplan PK was not evaluated by the pharmacometrics reviewer due to the small number of subjects positive for antipegcetacoplan antibodies in Phase 2 and 3 studies (refer to *Immunogenicity* above).

Figure 27. ETA-Covariate Plots for the Final PK Model



Source: Reviewer's plot based on the Applicant's final PopPK model.
Abbreviations: CL, clearance; ETA, estimate of interindividual variability; PK, pharmacokinetic; PopPK, population pharmacokinetic

14.3.3. Exposure-Response Analyses

Applicant's E-R for Hemoglobin and LDH Response in Patients With PNH

Objectives

- Develop a population E-R model to characterize the relationship between pegcetacoplan exposure and hemoglobin (Hb) level in patients with PNH.
- Evaluate the effects of selected intrinsic and extrinsic covariates as potential sources of variability in Hb response.
- Develop a population E-R model to characterize the relationship between pegcetacoplan exposure and LDH level in patients with PNH.
- Evaluate the effects of selected intrinsic and extrinsic covariates as potential sources of variability in LDH response.

Data

The population E-R analysis included dosing and Hb and LDH level data from four studies (two Phase 1b studies [CP0514 and APL2-204], one Phase 2a study [Study APL2-202], and one Phase 3 study [APL2-302]) in patients with PNH. Data from the Phase 3 Study APL2-302 were available up to Week 16 (Table 67).

Table 67. Summary of Studies and Sampling for PK, Hematology, Chemistry, and LDH

Study, Study Population, and Number Treated	Regimen and Doses	PK Sampling	Hematology and Chemistry, LDH Sampling
Study CP0514 PNH (eculizumab treated for ≥3 months), N=15 (12 pegcetacoplan)	Cohort 1: 25 mg SC ×1 followed by 28-day washout then 5 mg SC QD × 4 wks Cohort 2: 50 mg SC ×1 followed by 28 Days washout then 30 mg SC QD × 4 wks	Predose and 4 hr postdose on Day 1; Predose on Days 2, 3, 4, 8, 15, 22, 29, 43, 57, 71, 85, 113, and 141	Screening and Days 1, 8, 15, 22, 29, 43, 57, 71, 85, 113, and 141
	Cohort 3: 180 mg SC QD × 4 wks	Predose and 4 hr postdose on Day 1; Predose on Days 2, 3, 4, 8, 15, 22, 29, 43, 57, 71, 85, 113	Screening and Days 1, 8, 15, 22, 29, 43, 57, 71, 85, 113
	Cohort 4: Daily SC doses of 270 mg for up to 729 Days with optional intrasubject escalation up to 360 to 440 mg/day after Day 28	Predose and 4 hr postdose on Day 1; Predose on Days 2, 3, 4, 8, 15, 22, 29, 43, 57, 71, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 421, 477, 533, 617, 729, and 785	Screening and Days 1, 8, 15, 22, 29, 43, 57, 71, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 421, 477, 533, 617, 729, and 785
Study APL2-204 PNH (eculizumab naïve) N=23	Cohort 1: 180 mg SC QD ×4 wks Cohort 2: Daily SC doses of 270 mg for up to 414 Days with optional intrasubject escalation up to 360 mg/day	Predose and 2.5 hr postdose on Day 1; Predose on Days 2, 3, 8, 22, 29, 43, 71, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 379, 393, and 414	Screening and Days 1, 8, 15, 22, 29, 36, 43, 57, 71, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 379, 393, and 414 Additional LDH: Days 23 to 28
Study APL2-202 PNH (eculizumab naïve) N=4	270 mg SC QD × 4 wks, may increase up to 360 SC QD × up to 1 year	Predose and 2.5 hr postdose on Day 1; Predose (where applicable) on Days 2, 3, 8, 22, 29, 43, 71, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 379, 393, and 414	Screening and Days 1, 8, 15, 22, 29, 36, 43, 57, 71, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 379, 393, and 414
Study APL2-302 PNH (eculizumab treated) N=80 (41 pegcetacoplan; 39 eculizumab)	1,080 mg SC twice weekly or every 3 Days ×1 year	Predose (where applicable) on Days -28, -21, -14, 1, 14, 28, 42, 56, 84, and 112 Additional 6 hr postdose sample on Days 1, 28, and 112	Screening and Days -28, -21, -14, 1, 14, 28, 42, 56, 84, and 112

Source: Adapted from Applicant's E-R Report, Table 1, page 32.
Abbreviations: E-R, exposure-response; LDH, lactate dehydrogenase; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria; QD, once a day; SC, subcutaneous; wks, weeks

Methods

The modeling approach was identical for Hb and LDH. E-R model development followed a sequential approach where fitting of the E-R model was conditioned on individual predicted PK parameters estimated using the final PK model. Therefore, E-R model parameter estimation was based on observed Hb and LDH data and subject-level PK information propagated via individual predicted parameter estimates for CL, V2, and absorption rate. Population predicted PK parameters were used for those subjects who did not contribute a measurable PK sample.

Software

Analyses were performed using the nonlinear mixed-effects modeling methodology in NONMEM® (version 7.3). Data postprocessing and graphical analysis of data or output from the models was performed using Statistical Analysis System (version 9.4 or later) or R (version 3.5.2 or later).

Covariate Model

- **Hb E-R:** The covariates tested were female sex, Asian race, baseline C3, body weight, and CrCl on model-estimated population baseline Hb level; and female sex, individual observed baseline Hb level, baseline eculizumab, baseline C3, age, body weight, and CrCl on E_{max}. By the stepwise backward elimination procedure based on the likelihood ratio test, only individual observed baseline Hb level and CrCl on E_{max} were retained in the final E-R model.
- **LDH E-R**: The covariates tested were female sex, Asian race, baseline C3 level, age, and body weight on population baseline LDH; and Asian race, baseline C3 level, and body weight on EC_{50}. By the stepwise backward elimination procedure based on the likelihood ratio test, there were no covariates retained in the final model that were not included in the base model.

Applicant's Conclusions: E-R for Hemoglobin Response

The E-R relationship between pegcetacoplan concentration and Hb level was described by a sigmoidal direct effect model of E_{max}. The covariates included in the final E-R model for Hb were individual observed baseline Hb level and CrCl on E_{max}. Parameter estimates for the Hb final model are summarized in Table 68. GOF plots and VPC plots are presented in Figure 28 and Figure 29.

Table 68. E-R Parameter Estimates for the Hemoglobin Final Model

Theta / Parameter (Units)	Final Estimate	ASE	%RSE	95% CI	Preliminary Final Estimate	%Change in Estimate
15 BaseHb (g/dL)	8.59	0.0986	1.15	(8.40, 8.78)	8.59	0.00186
16 Emax	0.363	0.0211	5.82	(0.322, 0.405)	0.364	-0.0135
17 EC50 (µg/mL)	272	14.2	5.21	(244, 300)	273	-0.228
18 Hill	5.85	0.767	13.1	(4.35, 7.35)	5.76	1.56
29 BHb on Emax	-1.76	0.364	20.7	(-2.47, -1.05)	-1.75	0.728
34 CrCl on Emax	0.461	0.124	26.9	(0.218, 0.703)	0.457	0.721
Residual Variability						
19 RE Additive (g/dL)	1.01	0.0187	1.84	(0.978, 1.05)	1.02	-0.213
IIV (CV%)						
ETA4 – BaseHb	11.0%			(9.11%, 12.6%)	11.0%	0.298
ETA5 – Emax	45.8%			(34.1%, 54.8%)	45.6%	0.961
ETA6 – EC50	40.3%			(31.5%, 47.6%)	40.4%	-0.205
OFV	2615.948					

Source: Applicant's E-R analysis report, Table 14, page 60.
Abbreviations: ASE, asymptotic standard error; BaseHb, population baseline hemoglobin; BHb, individual baseline hemoglobin; CrCl, creatinine clearance; E-R, exposure-response; CI, confidence interval; CV, coefficient of variation; EC_{50}, half-maximal effective concentration; Emax, maximum proportional change from baseline; ETA, estimate of interindividual variability, Hill, sigmoidicity coefficient; IIV, interindividual variability; OFV, objective function value; RE, residual error; RSE, relative standard error

Figure 28. Hemoglobin Final Model Goodness-of-Fit Plots

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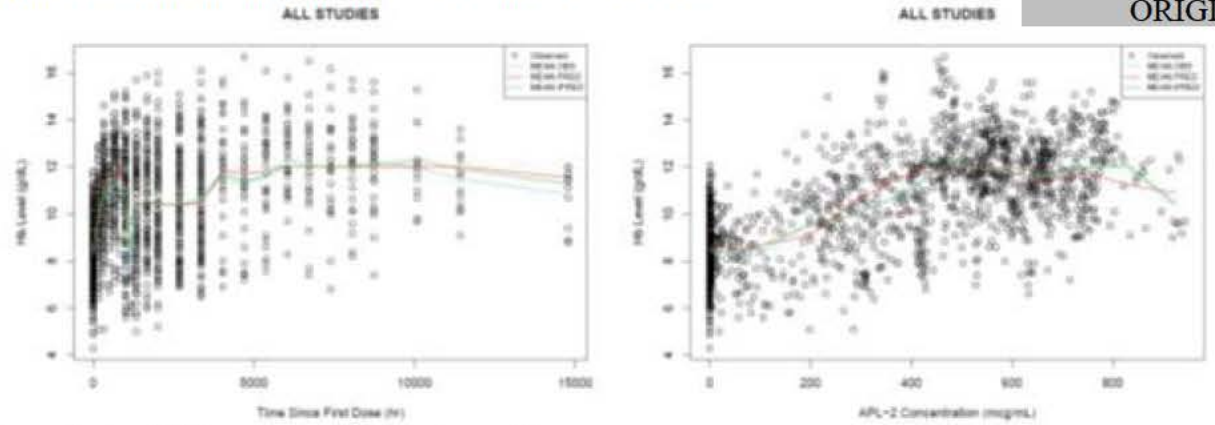
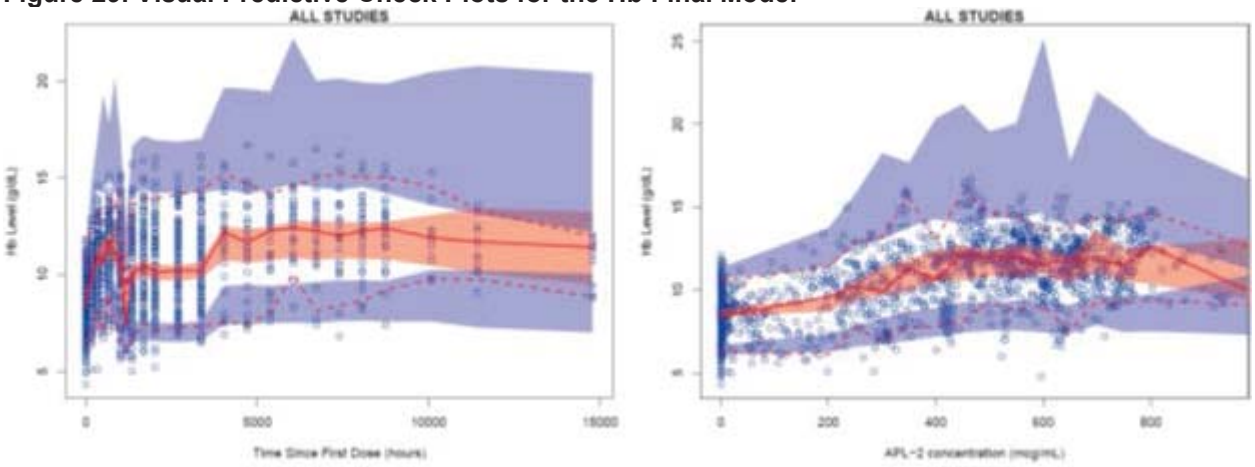


Source: Applicant's E-R analysis report, Figure 5, page 61.
Abbreviations: APL-2, pegcetacoplan; E-R, exposure-response; Hb, hemoglobin

Figure 29. Visual Predictive Check Plots for the Hb Final Model



Source: Applicant's E-R analysis report, Figure 6, page 62.
Abbreviations: APL-2, pegcetacoplan; E-R, exposure-response; Hb, hemoglobin

- The relationship between pegcetacoplan exposure and increase in Hb level was described using a sigmoidal E_{max} direct effect model. E_{max} was a 36.3% increase from baseline with an EC_{50} of 272 μg/mL.
- The median steady-state pegcetacoplan serum concentration associated with the dose regimen of 1,080 mg BIW is expected to achieve at least 99% of the maximal predicted Hb increase from baseline.
- Individual observed baseline Hb had an effect on E_{max}. Individuals with lower baseline Hb values are predicted to have a greater response, in terms of proportional increase in Hb from baseline. At the 5th percentile of individual baseline Hb (6.4 g/dL), E_{max} is predicted to be a 61.1% increase from baseline Hb and at the 95th percentile (10.6 g/dL) a 25.1% increase from baseline Hb is predicted.
- Baseline CrCl had an effect on E_{max}. Individuals with renal impairment at baseline are predicted to have a lesser response, in terms of the proportional increase in Hb from baseline. Steady-state Hb levels are predicted to be 12.8% lower at the 5th percentile of baseline CrCl (50 mL/min) and 12.0% higher at the 95th percentile (221 mL/min) relative to the median baseline CrCl of 120 mL/min.
- Sex, Asian race (including Japanese ethnicity), age, body weight, baseline eculizumab treatment status, and baseline C3 level are not anticipated to have meaningful effects on the Hb response to pegcetacoplan.
- Simulations of over- or under-delivery by 10% to 15% of the intended pegcetacoplan dose demonstrated that SC infusion dose delivery within this margin of error will not impact the steady-state Hb level relative to precise delivery of the intended dose (steady state Hb ratio 0.99 to 1.01).

Applicant's Conclusions: E-R for LDH Response

The E-R relationship between pegcetacoplan concentration and LDH level was described by a sigmoidal E_{max} direct effect model. Parameter estimates for the LDH final model are summarized

in Table 69. GOF plots and VPC plots are presented in the Applicant's E-R analysis report, Figure 12 (page 89) and Figure 13 (page 90).

Table 69. E-R Parameter Estimates for the LDH Final Model

Theta / Parameter (Units)	Estimate	ASE	%RSE	95% CI	Preliminary Final Estimate	%Change in Estimate
15 BaseLDH (IU/L)	2117	166	7.86	(1791, 2443)	2118	-0.0760
16 BaseLDH BECU (IU/L)	248	9.97	4.03	(228, 267)	248	0.0764
17 Emax	-0.908	0.00575	0.633	(-0.920, -0.897)	-0.909	-0.0370
18 Emax BECU	-0.325	0.0219	6.73	(-0.368, -0.282)	-0.324	0.317
19 EC50 (µg/mL)	173	17.4	10.1	(138, 207)	171	0.950
20 EC50 BECU (µg/mL)	250	24.5	9.80	(202, 298)	250	0.0493
21 Hill	3.84	0.433	11.3	(2.99, 4.69)	3.77	1.83
Residual Variability (%)						
22 RE	34.7	0. 654	1.88	(33.8, 36.0)	34.7	-0.0463
IIV (CV%)						
ETA4 - BaseLDH	33.8%			(28.6%, 38.4%)	33.8%	-0.0105
ETA6 - EC50	39.7%			(22.4%, 51.4%)	40.0%	-0.925
OFV	-1437.04					

Source: Applicant's E-R analysis report, Table 30, page 87.
Abbreviations: ASE, asymptotic standard error; BaseLDH, population baseline LDH; BECU, baseline eculizumab; E-R, exposure-response; CI, confidence interval; CV, coefficient of variation; EC_{50}, half-maximal effective concentration; Emax, maximum proportional change from baseline; ETA, estimate of interindividual variability, Hill, sigmoidicity coefficient; IIV, interindividual variability; LDH, lactate dehydrogenase; OFV, objective function value; RE, residual error; RSE, relative standard error

- The relationship between pegcetacoplan exposure and decrease in LDH level was described using a sigmoidal E_{max} direct effect model.
  - For patients without eculizumab treatment at baseline, E_{max} was a 90.8% decrease from a baseline of 2117 IU/L with an EC_{50} of 173 µg/mL
  - For patients on eculizumab treatment at baseline, E_{max} was a 32.5% decrease from a baseline of 248 IU/L with an EC_{50} of 250 µg/mL
- Steady-state pegcetacoplan serum concentrations with the dosing regimen of 1,080 mg BIW are expected to achieve at least 95% and 99% of the maximal predicted LDH response for subjects with and without eculizumab treatment at baseline, respectively, with 71.6% of all subjects predicted to achieve LDH levels below the upper limit of normal.
- Baseline eculizumab treatment status had an effect on baseline LDH, E_{max}, and EC_{50}. Median LDH levels at steady-state following pegcetacoplan 1,080 mg BIW are predicted to be 231 IU/L for eculizumab-naïve subjects versus 177 IU/L for subjects with eculizumab treatment at baseline, corresponding to 78.4% and 97.4% of eculizumab-naïve and -treated subjects achieving LDH control below 1.5-fold the upper limit of normal, respectively.

- Sex, Asian race (including Japanese ethnicity), age, body weight, baseline CrCl, and baseline C3 level are not anticipated to have meaningful effects on the LDH response to pegcetacoplan.
- Simulations of over- or under-delivery by 10% to 15% of the intended dose demonstrated that SC infusion dose delivery within this margin of error will not impact steady-state LDH level relative to precise delivery of the intended dose (steady-state LDH ratio 0.99 to 1.03).

Reviewer's Assessments of Exposure-Response in Patients With PNH

The key review questions were whether the E-R relationships supports the effectiveness of pegcetacoplan in the treatment of PNH in eculizumab-naïve patients, and whether the proposed dose is appropriate for all patients with PNH regardless of their eculizumab experience.

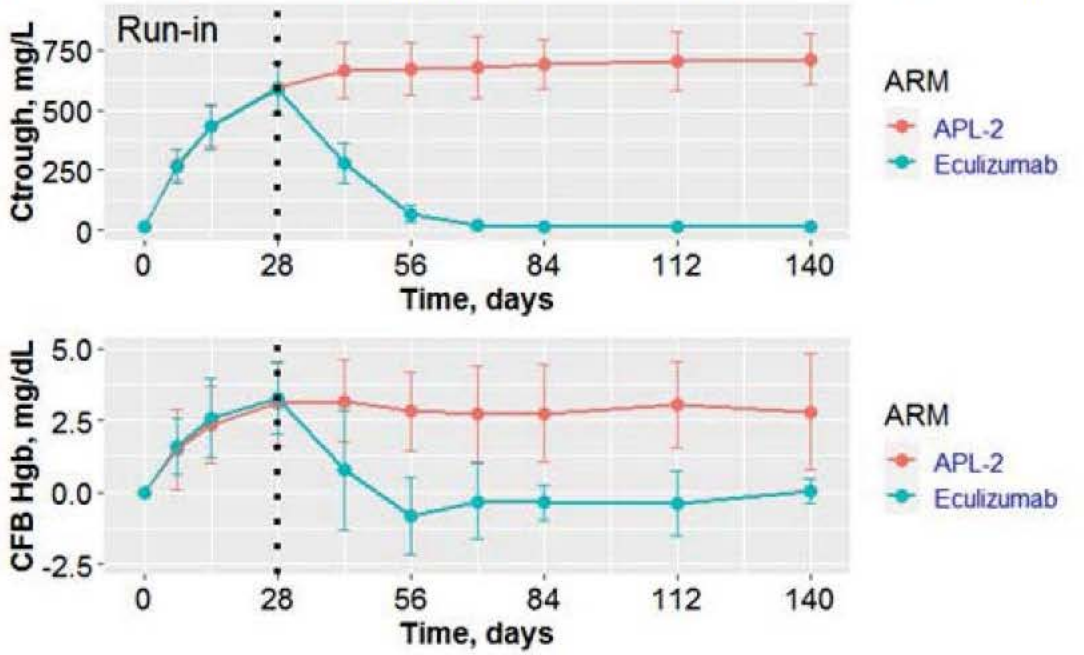
Exposure-Hemoglobin Response

Overall, the Applicant's E-R analysis adequately characterized the relationship between Hb response and time-matched concentrations of pegcetacoplan. At the proposed dose (1,080 mg BIW), the steady-state concentrations are expected to provide the maximum Hb response. E-R analysis did not identify significant difference in Hb response between eculizumab treated patients versus and patients who are not on eculizumab. The following components were assessed in detail by the reviewer:

- Use of a direct response model
  - The Applicant characterized the exposure-Hb relationship with a direct response model, which does not account for the potential time delay between PK and Hb change. However, the reviewer found that a direct model is acceptable because the studied dosing interval (once a day or BIW in clinical trials) is shorter than T_{max} (4 to 5 days) following SC administration and the effective half-life (~8 days). This led to a smaller peak-to-trough concentration ratio compared to the steady-state concentration of 650 ng/mL, which is reached at about 4 weeks. Hence, the data collected for PK and Hb from multiple-dose studies may not able to inform the indirect response model to capture the delay effect. This was also reported by the Applicant's attempt to fit an indirect response model, which resulted in poor precision of the turnover rate for Hb.

    Also, the time course of Hb response follows a similar trajectory to the predose concentrations observed in the Phase 3 study (Figure 30). Particularly, in the patients in eculizumab group who received pegcetacoplan along with eculizumab for 4 weeks during the run-in period, then discontinued pegcetacoplan, the trajectories for the lowest concentration and Hb response are similar. This supports the ability of the parsimonious direct response model to describe the E-R relationship for Hb response.

Figure 30. Mean Observed C_{trough} (Top) and Change From Baseline in Hb (Bottom), APL2-302

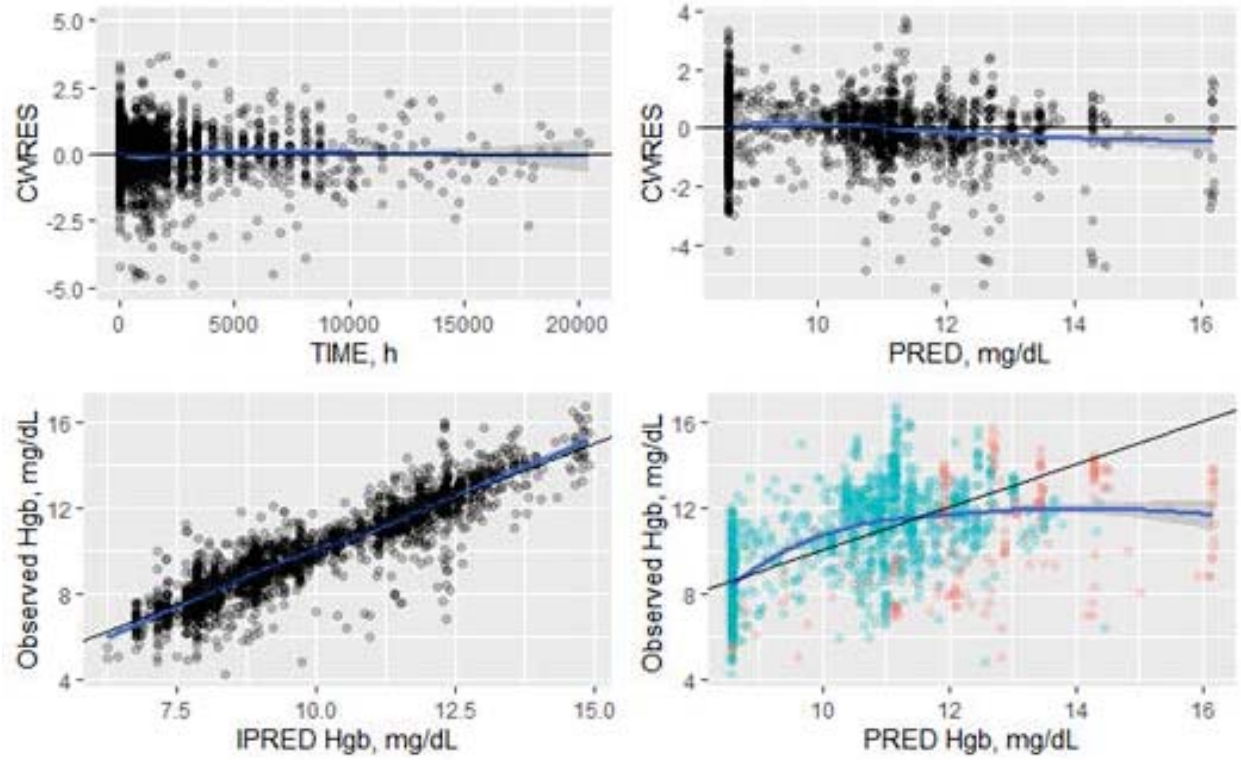


Source: Reviewer's figure based on ADPC.xpt (top) and ADEFF.xpt (bottom). The hemoglobin response (bottom) summary was censored for transfusions.
Vertical bars represent standard errors.
Abbreviations: APL-2, pegcetacoplan; CFB, change from baseline; C_{trough}, lowest concentration

Model Adequacy

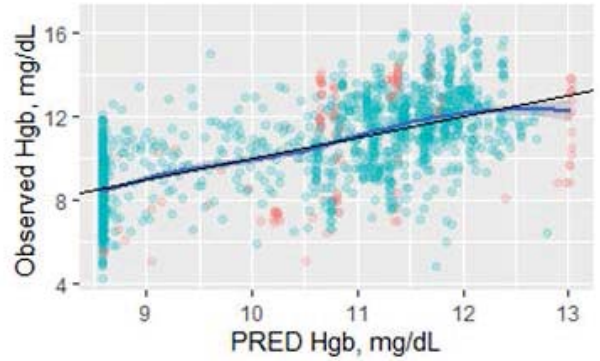
GOF plots (Figure 31) show good agreements between individual predicted concentrations and individual observed Hb levels. Parameter estimates are estimated with acceptable precisions. VPC plots in general captured the observed data and variability. However, an overprediction of population prediction was noted in predicted concentrations versus observed Hb at higher Hb range (Figure 31, bottom right). This bias appears to be driven by the subjects with low baseline Hb levels (i.e., <7 g/dL), which indicates that the power model (i.e., $E_{max} \sim$ typical $E_{max} \times (\text{baseline Hb} \div 8.6)^{-1.76}$) may not be able to describe the covariate-parameter relationship. When the parameters were re-estimated after the Hb covariate effect from E_{max} was removed from the model, this bias was not observed (Figure 32). The parameter estimates for structural parameters (baseline Hb, E_{max}, EC_{50}) were largely unchanged although there was an increase in IIV on E_{max} (54% versus 46% in the final model). This suggests that the noted bias in covariate effect is not likely to affect the population E_{max} or EC_{50}, preserving the shapes of E-R relationships.

Figure 31. Standard GOF for the Applicant's Final Hemoglobin E-R Model



Source: Reviewer's plot.
For the plot of observed Hgb versus PRED, blue dots represent baseline Hgb >7 mg/dL and red dots, baseline Hgb <7 mg/dL.
Abbreviations: CWRES, conditioned weight residuals; E-R, exposure-response; GOF, goodness-of-fit; Hgb, hemoglobin; IPRED, individual predicted concentrations; PRED, predicted concentrations

Figure 32. Observed Hgb Versus PRED After Removing Covariate Model From the Final Model



Source: Reviewer's plot.
For the plot of observed Hgb versus PRED, blue dots represent baseline Hgb >7 mg/dL and red dots, baseline Hgb <7 mg/dL.
Abbreviations: Hgb, hemoglobin; PRED, predicted concentrations

Exposure-LDH Response

The Applicant's E-R analysis suggests that the E-R relationships for LDH differ between eculizumab-experienced and -naïve patients. This difference is mainly driven by the different baseline LDH levels between these patient groups. In the patients who were on eculizumab, LDH was already controlled and initiating treatment with pegcetacoplan further decreased LDH level by 33% resulting in an ending LDH level of 177 IU/L. In contrast, in patients not on eculizumab, LDH levels were elevated almost 10-fold compared to the upper limit of normal (226 IU/L). Pegcetacoplan treatment in the treatment-naïve patients resulted in a 90% reduction in LDH level, for an ending LHD level of 231 IU/L. Although E_{max} differed depending on the use of eculizumab at baseline, the EC_{50} estimates were similar between treatment-naïve (250 µg/mL) and -experienced (173 µg/mL) patients. This suggests that similar to the Hb response, the proposed dose is expected to provide a maximal effect on LDH control for both eculizumab-naïve and -experienced patients with PNH.

14.4. Summary of Bioanalytical Method Validation and Performance

Bioanalytical Methods for the Measurement of Serum Pegcetacoplan

Four high-performance liquid chromatography with tandem mass spectrometry methods were developed and validated for the quantitative determination of pegcetacoplan concentrations in human serum in the completed clinical studies. Details of the methods and validation parameters are listed in Table 70 to Table 73. Standard curve linearity, selectivity/specificity, assay accuracy and precision, extraction efficiency, and dilution fulfilled the standard acceptance criteria. The established frozen storage stability and run storage stability covered the corresponding study period and sample analysis period. The reviewers deemed that the method validation and sample analysis are acceptable.

Table 70. Validation Parameters for Method BIO.VR.0210-1989

Parameter	Information
Method validation report	BIO.VR.0210-1989.01, BIO.VR.0210-1989.02, BIO.VR.0210-1989.03
Study	APL2-302
Methodology	The analyte (pegcetacoplan/APL-2) and internal standard (APL-2-D22) were extracted from 50 µL of human serum by protein precipitation using acetonitrile. The supernatant was diluted and analyzed by LC-MS/MS.
Calibration curve range	10.0 to 1000 µg/mL
Accuracy (% bias)	
Inter-run	-3.5% to 0.3% (3% at the LLOQ)
Intrarun	-2.5% to 1.7 % (5% at the LLOQ)
Precision (%CV)	
Inter-run	2.6% to 3.7% (5.9% at the LLOQ)
Intrarun	2.2% to 3.8% (6.9% at the LLOQ)
Long-term stability	555 Days at -20°C
Processed extract stability	69 hr at room temperature
Freeze-thaw stability	Demonstrated for four cycles at ≤-20ºC
Analyte recovery	94.4 to 104.3% for pegcetacoplan and 90.5 to 93.0% for APL-2-D22

Source: Applicant's Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 4.
Abbreviations: CV, coefficient of variation; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantitation

Table 71. Validation Parameters for Method ALM-075

Parameter	Information
Method validation report	VAL075
Studies	CP0713-1, APL2-CP1014, APL2-401, APL2-101, APL2-205, APL2-202, and APL2-204
Methodology	The analyte (pegcetacoplan) and internal standard (APL-2-D22) were extracted from 100 µL of human serum by protein precipitation using acetonitrile. The supernatant was filtered, evaporated to dryness, reconstituted, and analyzed by LC-MS/MS.
Calibration curve range	0.100 to 10.0 µg/mL
Dilutions established	1:10, 1:20, and 1:50
Accuracy (% bias)	
Inter-run	-1.7% to 0% (2.0% at the LLOQ)
Intrarun	-0.1 to 8.7 % (6.0% at the LLOQ)
Precision (%CV)	
Inter-run	4.6% to 9.5% (10.9% at the LLOQ)
Intrarun	4.7% to 8.9% (10.1% at the LLOQ)
Long-term stability	94 Days at -20°C and 223 Days at -80°C
Processed extract stability	66 hr at room temperature
Freeze-thaw stability	Demonstrated for three cycles at ≤-20ºC
Analyte recovery	111.0% to 122.4% for pegcetacoplan and 111.8% for APL-2-D22

Source: Applicant's Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 4.
The validation parameters dilution integrity, selectivity, recovery, and stability were assessed by another laboratory (b) (4) (b) (4) Study ID MV-2014-914).
Abbreviations: CV, coefficient of variation; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantitation

Table 72. Validation Parameters for Method BPAPL2F

Parameter	Information
Method validation report	ARAPL2F
Study	CP0514
Methodology	The analyte (pegcetacoplan) and internal standard (APL-2-D22) were extracted from 100 µL of human serum by protein precipitation using acetonitrile. The supernatant was filtered, evaporated to dryness, reconstituted, and analyzed by LC-MS/MS.
Calibration curve range	0.100 to 10.0 µg/mL
Dilutions established	1:10, 1:20, and 1:50
Accuracy (% bias)	
Inter-run	-4.85% to -1.03% (3.86% at the LLOQ)
Intrarun	2.78% to 3.94% (9.92% at the LLOQ)
Precision (CV%)	
Inter-run	≤8.59% 8.67% at the LLOQ
Intrarun	≤7.19% 9.10% at the LLOQ
Long-term stability	339 Days at -20°C and at -80°C
Processed extract stability	57 hr at room temperature
Freeze-thaw stability	Demonstrated for three cycles at ≤ -20ºC
Analyte recovery	111 % to 122% for pegcetacoplan and 112% for APL-2-D22

Source: Applicant's Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 4.
Abbreviations: CV, coefficient of variation; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantitation

Table 73. Validation Parameters for Method ARAPL2K

Parameter	Information
Method validation report	ARAPL2K
Study	APL2-102
Methodology	The analyte (pegcetacoplan) and internal standard (APL-2-D22) were extracted from 50 µL of human serum by protein precipitation using acetonitrile. The supernatant was then diluted and analyzed by LC-MS/MS.
Calibration curve range	5.00 to 500 µg/mL
Dilutions established	1:10, 1:20, and 1:50
Accuracy (% bias)	
Inter-run	–2.92% to 7.18% (–10.6% at the LLOQ)
Intrarun	1.56% to 12.0% (–11.6% at the LLOQ)
Precision (%CV)	
Inter-run	≤6.59% (8.67% at the LLOQ)
Intrarun	≤5.82% (11.3% at the LLOQ)
Long-term stability	343 Days at -20°C and at -70°C
Processed extract stability	57 hr at room temperature
Freeze-thaw stability	Demonstrated for four cycles at ≤ -20°C
Analyte recovery	89.5% to 107% for pegcetacoplan and 99.5% for APL-2-D22

Source: Applicant's Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 4.
A method was previously validated for pegcetacoplan in human serum at a dynamic range of 0.100 to 10.0 µg/mL (ARAPL2F). A partial validation study was conducted to modify the dynamic range to 5.00 to 500 µg/mL and reported herein.
Abbreviations: CV, coefficient of variation; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantitation

Bioanalytical Methods for the Measurement of PD Biomarkers

PD biomarkers of serum C3 levels, proportions of PNH Type II and III RBCs, and C3 deposition on these RBCs were determined using a flow cytometric method developed at (b) (4) (b) (4) and validated at (b) (4) (b) (4) as a laboratory-developed test (Table 74). This assay yields both quasi-quantitative and qualitative reportable results. Because the results of PD biomarkers are reported as changes from baseline, rather than absolute values, these semiquantitative bioanalytical methods for PD markers are acceptable.

Table 74. Validation Summary for Bioanalytical Methods for PD Markers

Validation Report	Method Description and Performance
Validation Report for the BNII Complement C3 Assay Document number: December 2007, December 2014, and July 2017	C3 human serum Flow cytometry method Complement C3 was performed on the Dade Behring BN II analyzer. The Dade Behring BN II assay is an immunochemical reaction where C3 contained in the human serum sample forms immune complexes with specific antibodies Limit of quantification: 13 mg/dL Intra-assay precision (%CV): 2.4 to 4.6 Interassay precision (%CV): 4.1 to 5.3 Stability in human serum: Long-term freezer storage stability: 4 months at -70°C Freeze-thaw stability at -70°C: two cycles

Validation Report	Method Description and Performance
Validation Report: 573697	PNH Panel 2 Flow cytometry method PNH Panel 2 (CD59, CD235a, and C3d) is a flow cytometric method designed for the characterization of PNH-associated abnormal RBCs in peripheral whole blood. The method was developed at (b) (4) Limit of detection: Type II RBC: relative percentage: 0.063%, number of events: 55 Type III RBC: relative percentage: 0.020%, number of events: 16 C3d+Type II RBC: relative percentage: 0.000%, number of events: 4 C3d+Type III RBC: relative percentage: 0.000%, number of events: 3 Limit of quantification: Type II RBC: relative percentage: 0.070%, number of events: 59 Type III RBC: number of events: 70 Intra-assay precision (%CV): Type II RBC: 17.4 Type III RBC: 7.14 C3d+Type II RBC: 29.1 C3d+Type III RBC: 3.31 Interassay precision (%CV): RBC: 0.076 GlyA+RBC: 0.033

Source: Applicant's Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 4
Abbreviations: C, complement protein; CD, cluster of differentiation; CV, coefficient of variation; GlyA, glycophorin A; PD, pharmacodynamic; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell

Bioanalytical Methods for Monitoring Immunogenicity

To assess the immunogenicity risk for pegcetacoplan, Applicant developed anti-drug antibody (ADA) assays to detect antibodies against the functional peptide or the PEG portion of pegcetacoplan. Patient samples were screened for the presence of ADA using the screening assay. The screened positive samples were then tested in the confirmatory assay and those confirmed positive were characterized for the ADA titer. Applicant also developed a neutralizing anti-drug antibody (NAb) assay to assess the neutralizing activity of detected ADA. Although the reported sensitivity of the screening assay for antibodies to the functional peptide moiety is lower than the minimal sensitivity recommended by current FDA guidance, 500 ng/mL[Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products—Developing and Validating Assays for Anti-Drug Antibody Detection, January 2019" https://www.fda.gov/media/119788/download], review of the assays showed that neither the screening nor the neutralizing assays were sufficiently sensitive due to on-board drug interference. The low drug tolerance of the anti-pegcetacoplan peptide antibody and neutralizing antibody assays and the limited immunogenicity data available (up to 16 weeks) precluded an adequate analysis of the incidence of ADA, their neutralizing activity, and their impact on PK, PD, efficacy, or safety of pegcetacoplan. Details regarding the validation of immunogenicity assay can be found in the Office of Biotechnology Products (OBP) review by Dr. Marco Cardone and Dr. Daniela Verthelyi in the Document Archiving, Reporting and Regulatory Tracking System on May 10, 2021. To address these issues, three PMCs were proposed (see Section 23).

15. Trial Design: Additional Information and Assessment

15.1. Protocol Amendments

The clinical protocol for Study APL2-302 was amended four times. An overview of each amendment is provided in Table 75.

Table 75. Overview of Protocol Amendments, APL2-302

Amendment Number and Date	Summary of Significant Changes
Amendment 1 August 21, 2018	Schedule of Events was amended to include: • Upon confirmation of study eligibility from the Visit 1 screening assessments, patients in Study APL2-302 may proceed to Visit 2 at any time. • Eculizumab/pegcetacoplan combination treatment for both groups may extend until the end of Day 1. Inclusion criteria were added to: • Require that subjects have a BMI ≤40 to qualify for study entry. • Indicate that subjects are eligible for the study if they have an ARC >1× ULN at the screening visit. Pregnancy was added as a criterion for study discontinuation. Exclusion criteria were added to: • Indicate that any active bacterial infection must be resolved within 1 week of Day -28 (the first dose of pegcetacoplan).
Amendment 2 December 13, 2018	Modifications were made to the Schedule of Events: • Procedures for the administration of eculizumab and pegcetacoplan during study visits were clarified in the Study Procedures section. • During screening, if a subject's screening visit is completed greater than 28 Days prior to dosing, a hematology panel should be repeated within 28 Days of dosing to confirm patient eligibility.
Amendment 3 February 8, 2019	Key secondary endpoints were established. Former tertiary endpoints were reclassified as secondary endpoints. Due to changes in the key secondary endpoints, the comparator-control period was modified to Day 1 to Week 16. The study diagram in the study design section was modified to remove references to the wash-out period. Minor global edits for clarity or to correct errors were made including reference to the 16-week RCP, which was previously described as the randomized-comparator-control period. Inclusion criteria modified to exclude subjects with Class 2 or greater obesity from enrolling in the study.

Amendment Number and Date	Summary of Significant Changes
Amendment 4 August 16, 2019	Schedule of events was modified: • Clarification of *Streptococcus pneumoniae* vaccination requirement scenarios • Prerandomization transfusion history collection requirements clarified. Pegcetacoplan dose adjustment were updates to mandate dose escalation upon the first instance of subject reporting of LDH >2× ULN to pegcetacoplan 1,080 mg every third day. In the event of a dose increase, LDH will be monitored twice a week for at least 4 weeks to assess the impact of the dose adjustment on LDH levels.

Source: Clinical reviewer's table summarizing the Clinical Study Report.
Abbreviations: ARC, absolute reticulocyte count; BMI, body mass index; LDH, lactate dehydrogenase; RCP, randomized control period; ULN, upper limit of normal

15.2. Protocol Deviations

The Applicant defined a protocol deviation to be major if it significantly impacted subject safety and/or data integrity, defines as variation and/or omission from the approved study protocol, whether intentional or unintentional that may significantly adversely affect the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the data.

Per the Applicant, in Study APL2-302, 59 (73.8%) patients had protocol deviations determined to be major deviations, as defined above. A similar percentage of these was from each treatment group. Most major protocol deviations (45 patients; 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.

Twelve patients had a major protocol deviation involving eligibility criteria (six in the pegcetacoplan group and six in the eculizumab group). Five patients (two in the pegcetacoplan group and three in the eculizumab group) had a protocol deviation due to prohibited concomitant medications, all considered major. All were related to initiation of corrected QT interval (QTc)-prolonging medications without being on a stable dose for at least 3 weeks prior to pegcetacoplan dosing. Two subjects in the pegcetacoplan group and two in the eculizumab group received ciprofloxacin. One patient in the eculizumab group received a single IV dose of promethazine.

Two patients in the eculizumab group had major protocol deviations related to safety reporting errors. Subject (b) (6) had a missing serious adverse event (SAE) initial report and follow-up report because of faxing error. For Subject (b) (6), the site did not send the SAE initial report until 48 hr after the SAE.

Five patients (6.3%) had major protocol deviations related to study drug noncompliance (three subjects in the pegcetacoplan group and two in the eculizumab group). Two patients had major protocol deviations related to missing one dose of study medication and three patients had major deviations related to receiving study drug outside of the regular dosing schedule.

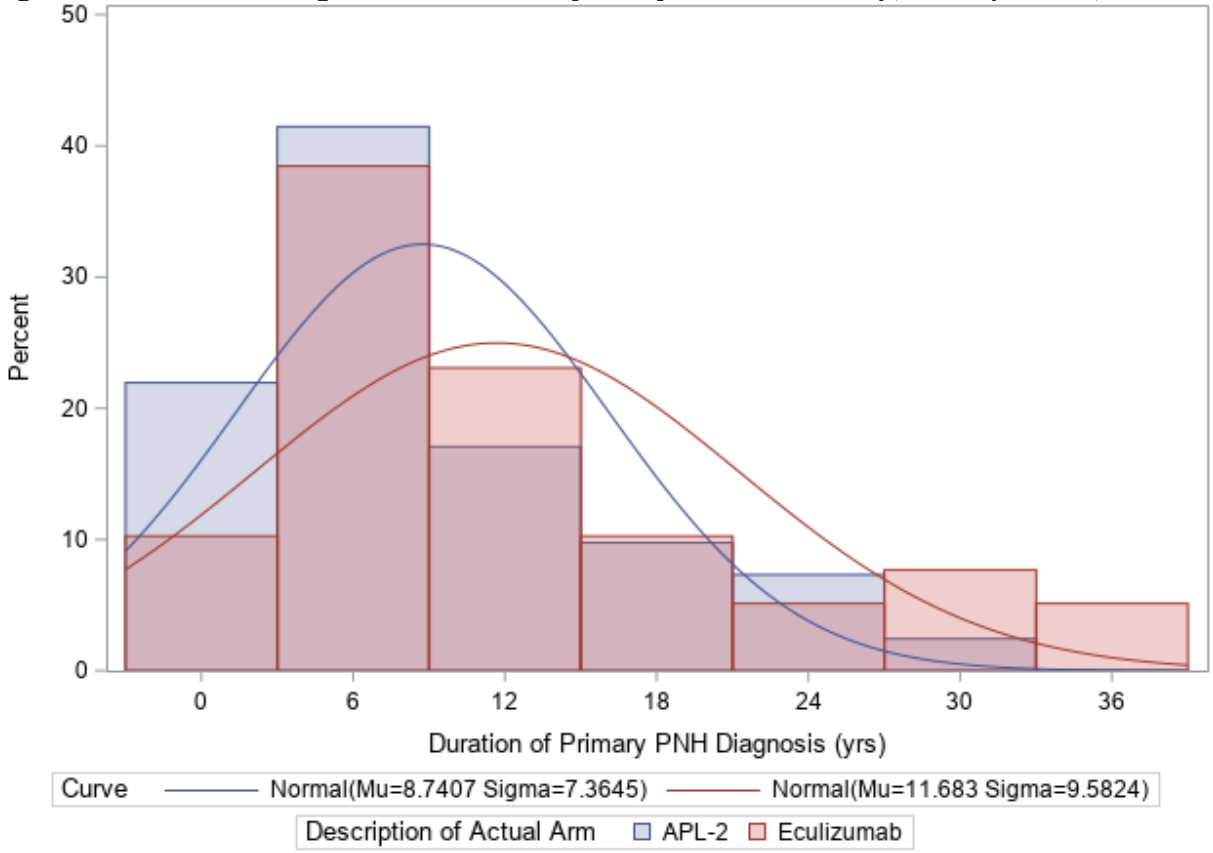
Three patients had major deviations due to nonadherence to protocol-specified criteria for packed RBC (PRBC) transfusion (all three in the eculizumab group). Six subjects were excluded from the per protocol set because of violations of inclusion or exclusion criteria and/or deviations from the protocol that were deemed to have potential to influence their efficacy assessment (two in the pegcetacoplan group and four in the eculizumab group). The reasons for exclusion from the per

protocol set included enrollment and inclusion/exclusion deviations (three patients) and test/assessment/procedure deviations (three patients).

16. Efficacy: Additional Information and Assessment

16.1. Supplemental Efficacy Tables and Figures

Figure 33. Time Since Diagnosis of PNH to Day -28 by Treatment Group, ITT Population, APL2-302



Source: Statistical reviewer's analysis.
Abbreviations: APL-2, pegcetacoplan; ITT, intent-to-treat; Mu, mean; PNH, paroxysmal nocturnal hemoglobinuria; Sigma, standard deviation; yrs, years

Table 76. CFB in Hb Level During RCP, ITT Population, APL2-302

Week	Pegcetacoplan 1,080 mg N=41 LSM CFB (g/dL)[1] (95% CI)	Eculizumab N=39 LSM CFB (g/dL)[1] (95% CI)	Pegcetacoplan and Eculizumab Difference in LSM (95% CI)
Week 2	3.07 (2.49, 3.64)	0.83 (0.22, 1.44)	2.24 (1.45, 3.03)
Week 4	2.78 (2.28, 3.28)	-1.50 (-2.09, -0.91)	4.28 (3.56, 5.00)
Week 6	2.68 (2.10, 3.25)	-1.51 (-2.33, -0.69)	4.19 (3.23, 5.14)
Week 8	2.38 (1.77, 3.00)	-1.74 (-2.65, -0.83)	4.12 (3.07, 5.18)
Week 12	2.75 (2.18, 3.33)	-1.57 (-2.42, -0.73)	4.33 (3.34, 5.31)
Week 16	2.37 (1.63, 3.10)	-1.47 (-2.81, -0.13)	3.84 (2.33, 5.34)

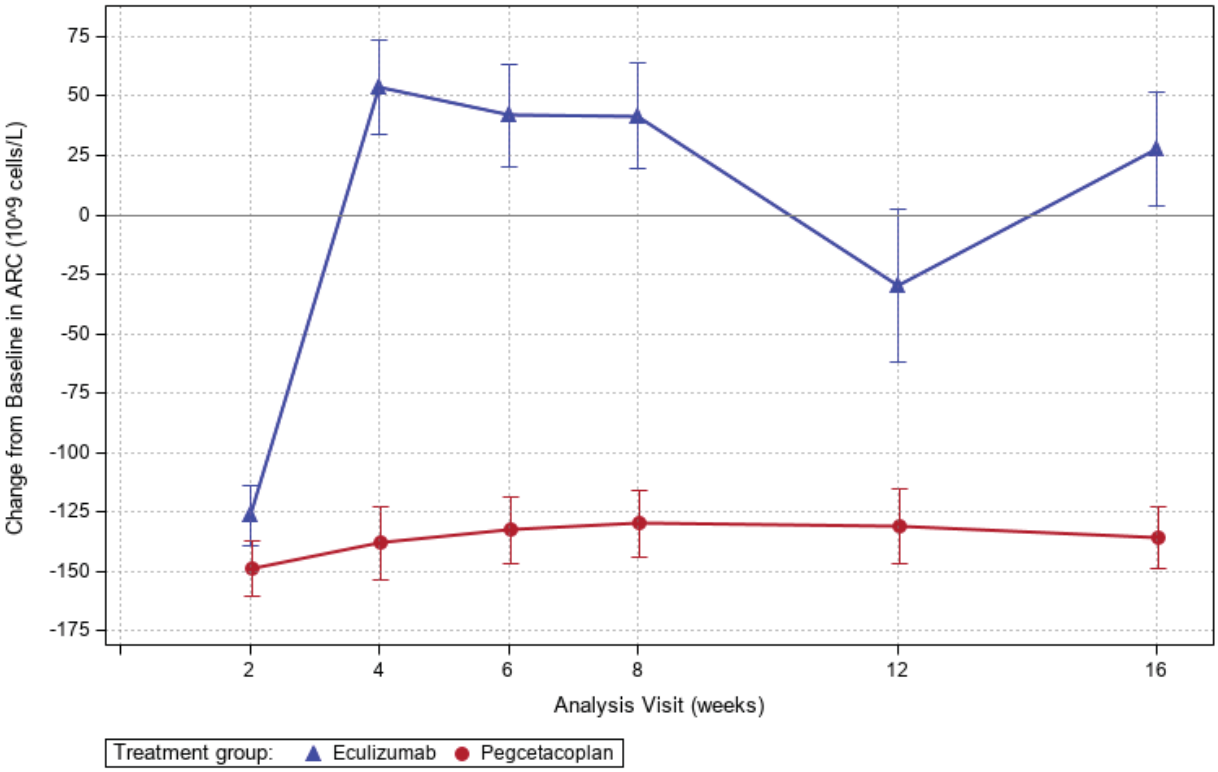
Source: Study APL2-302 Clinical Study Report, Table 21 (p. 104); statistical reviewer's analysis.
[1] Endpoint values after transfusion and study withdrawal were set to missing.
Results are based on a mixed model for repeated measures, which included the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.
Abbreviations: CFB, change from baseline; CI, confidence interval; Hb, hemoglobin; ITT, intent-to-treat; LSM, least squares mean; N, number of patients; RCP, randomized control period

Table 77. CFB in ARC During RCP, ITT Population, APL2-302

Week	Pegcetacoplan 1,080 mg N=41 LSM CFB (10^9 Cells/L)[1] (95% CI)	Eculizumab N=39 LSM CFB (10^9 Cells/L)[1] (95% CI)	Pegcetacoplan and Eculizumab Difference in LSM (95% CI)
Week 2	-148.88 (-160.72, -137.03)	-126.42 (-139.07, -113.77)	-22.46 (-38.72, -6.20)
Week 4	-138.11 (-153.75, -122.47)	53.64 (33.60, 73.69)	-191.76 (-216.51, -167.00)
Week 6	-132.54 (-146.62, -118.45)	41.86 (20.54, 63.18)	-174.40 (-199.25, -149.55)
Week 8	-129.91 (-144.13, -115.68)	41.71 (19.62, 63.80)	-171.62 (-197.20, -146.03)
Week 12	-131.17 (-146.76, -115.59)	-29.63 (-61.58, 2.31)	-101.54 (-136.51, -66.57)
Week 16	-135.82 (-149.01, -122.63)	27.79 (4.11, 51.46)	-163.61 (-189.91, -137.30)

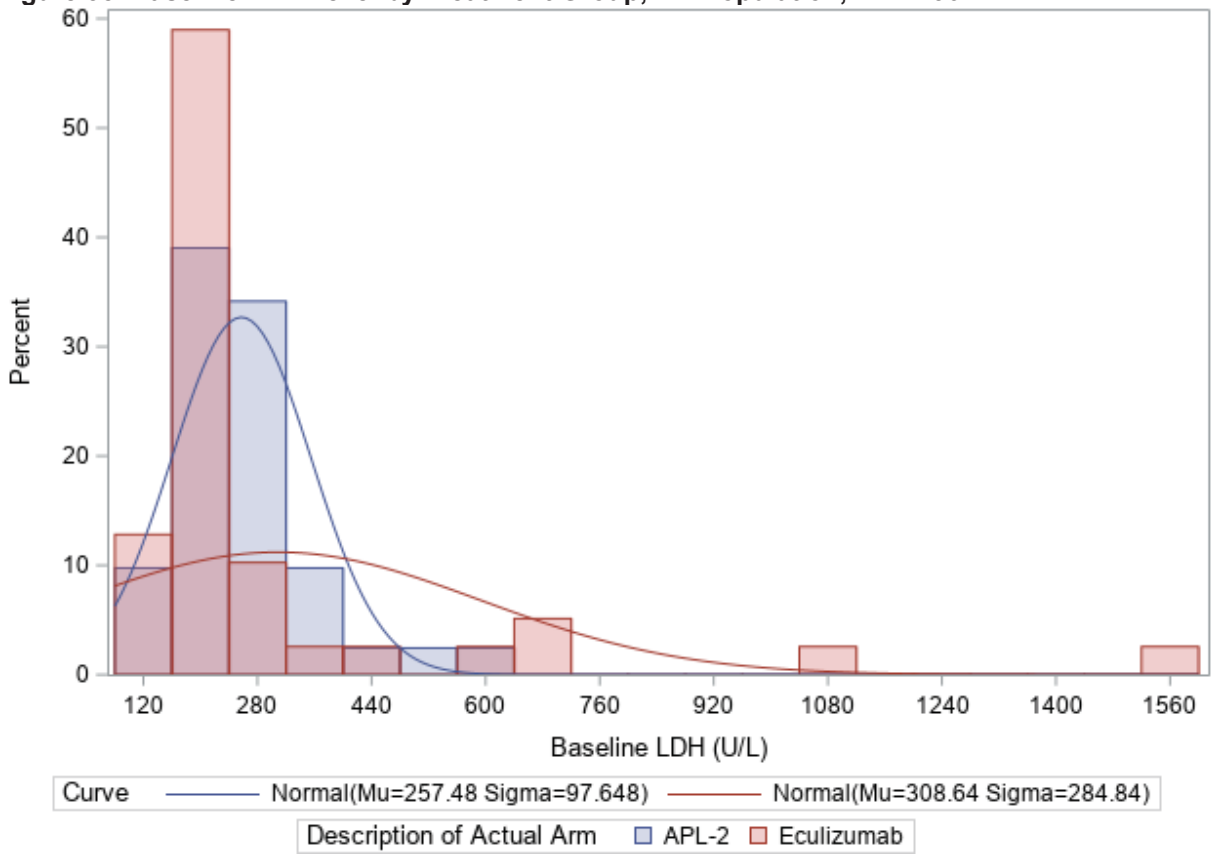
Source: Study APL2-302 Clinical Study Report, Table 29 (p. 115); statistical reviewer's analysis.
[1] Endpoint values after transfusion and study withdrawal were set to missing.
Results are based on a mixed model for repeated measures which included the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.
Abbreviations: ARC, absolute reticulocyte count; CFB, change from baseline; CI, confidence interval; ITT, intent-to-treat; LSM, least squares mean; N, number of patients; RCP, randomized control period

Figure 34. Mean CFB in ARC During RCP by Visit and Treatment Group, ITT Population, APL2-302



Note: Treatment effect estimates from a mixed model are shown.
Note: The mixed model contained the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.
Note: Vertical lines represent 95% confidence intervals for least squares mean estimates.
Source: Statistical reviewer's analysis.
Endpoint values after transfusion and study withdrawal were set to missing.
Abbreviations: ARC, absolute reticulocyte count; CFB, change from baseline; ITT, intent-to-treat; RCP, randomized control period

Figure 35. Baseline LDH Level by Treatment Group, ITT Population, APL2-302



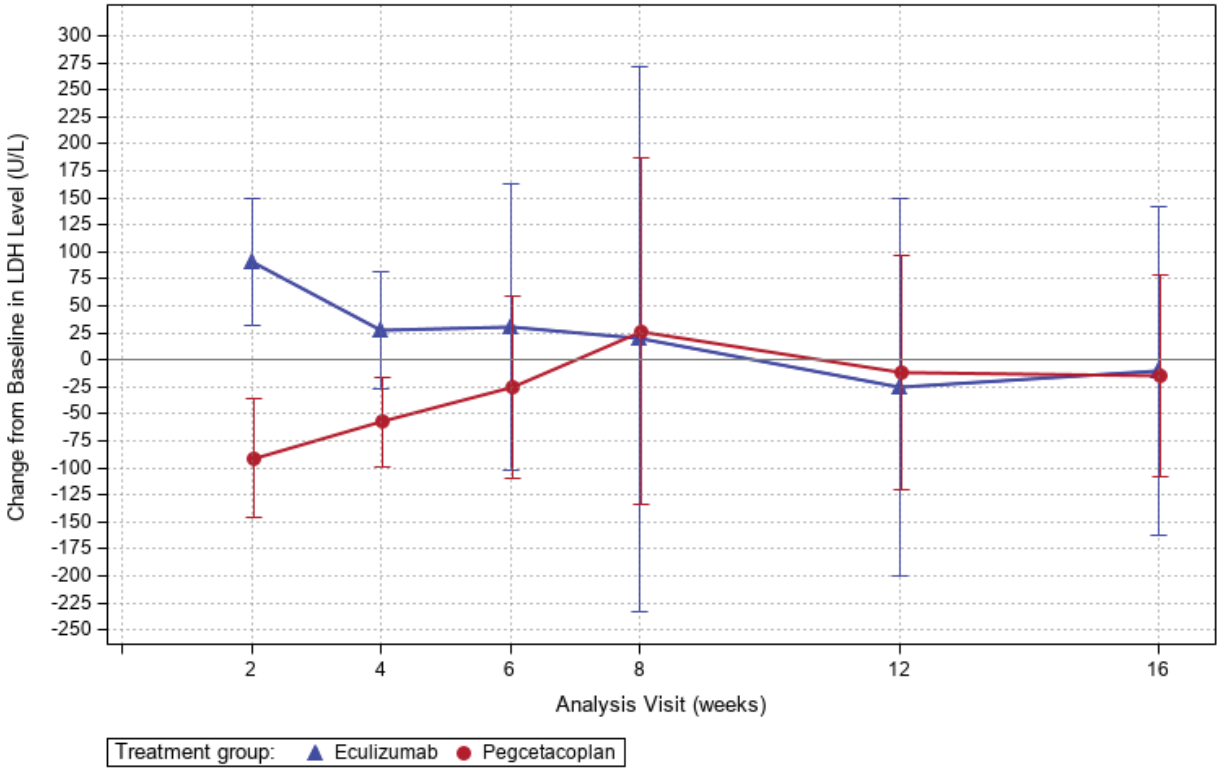
Source: Statistical reviewer's analysis.
Abbreviations: APL-2, pegcetacoplan; ITT, intent-to-treat; LDH, lactate dehydrogenase; Mu, mean; Sigma, standard deviation

Table 78. CFB in LDH Level During RCP, ITT Population, APL2-302

Week	Pegcetacoplan 1,080 mg N=41 LSM CFB (U/L)[1] (95% CI)	Eculizumab N=39 LSM CFB (U/L)[1] (95% CI)	Pegcetacoplan and Eculizumab Difference in LSM (95% CI)
Week 2	-90.99 (-146.20, -35.77)	90.09 (31.36, 148.82)	-181.08 (-257.68, -104.47)
Week 4	-57.57 (-99.08, -16.06)	27.28 (-27.41, 81.97)	-84.85 (-148.47, -21.23)
Week 6	-24.83 (-109.11, 59.46)	30.12 (-102.56, 162.80)	-54.94 (-210.01, 100.13)
Week 8	26.05 (-134.30, 186.41)	19.28 (-232.94, 271.49)	6.77 (-290.68, 304.23)
Week 12	-11.11 (-119.47, 97.26)	-24.68 (-199.28, 149.92)	13.57 (-190.18, 217.32)
Week 16	-14.76 (-107.94, 78.43)	-10.12 (-162.29, 142.04)	-4.63 (-181.30, 172.04)

Source: Study APL2-302 Clinical Study Report, Table 31 (p. 118); statistical reviewer's analysis.
[1] Endpoint values after transfusion and study withdrawal were set to missing.
Results are based on a mixed model for repeated measures, which included the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.
Abbreviations: CFB, change from baseline; CI, confidence interval; ITT, intent-to-treat; LDH, lactate dehydrogenase; LSM, least squares mean; N, number of patients; RCP, randomized control period

Figure 36. Mean CFB in LDH Level During RCP by Visit and Treatment Group, ITT Population, APL2-302



Note: Treatment effect estimates from a mixed model are shown.
Note: The mixed model contained the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.
Note: Vertical lines represent 95% confidence intervals for least squares mean estimates.

Source: Statistical reviewer's analysis.
Endpoint values after transfusion and study withdrawal were set to missing.
Abbreviations: CFB, change from baseline; ITT, intent-to-treat; LDH, lactate dehydrogenase; RCP, randomized control period

Table 79. CFB in LDH Level at Week 16 of RCP, ITT Population, APL2-302

Parameter	Value
LSM CFB in LDH (U/L)[1] (95% CI)	
Pegcetacoplan 1,080 mg, N=41	-14.17 (-77.07, 48.73)
Eculizumab, N=37	-47.94 (-150.18, 54.29)
Difference in LSM between pegcetacoplan and eculizumab (95% CI)	33.78 (-85.34, 152.89)
Nominal p-value for difference in LSM[2]	0.5642

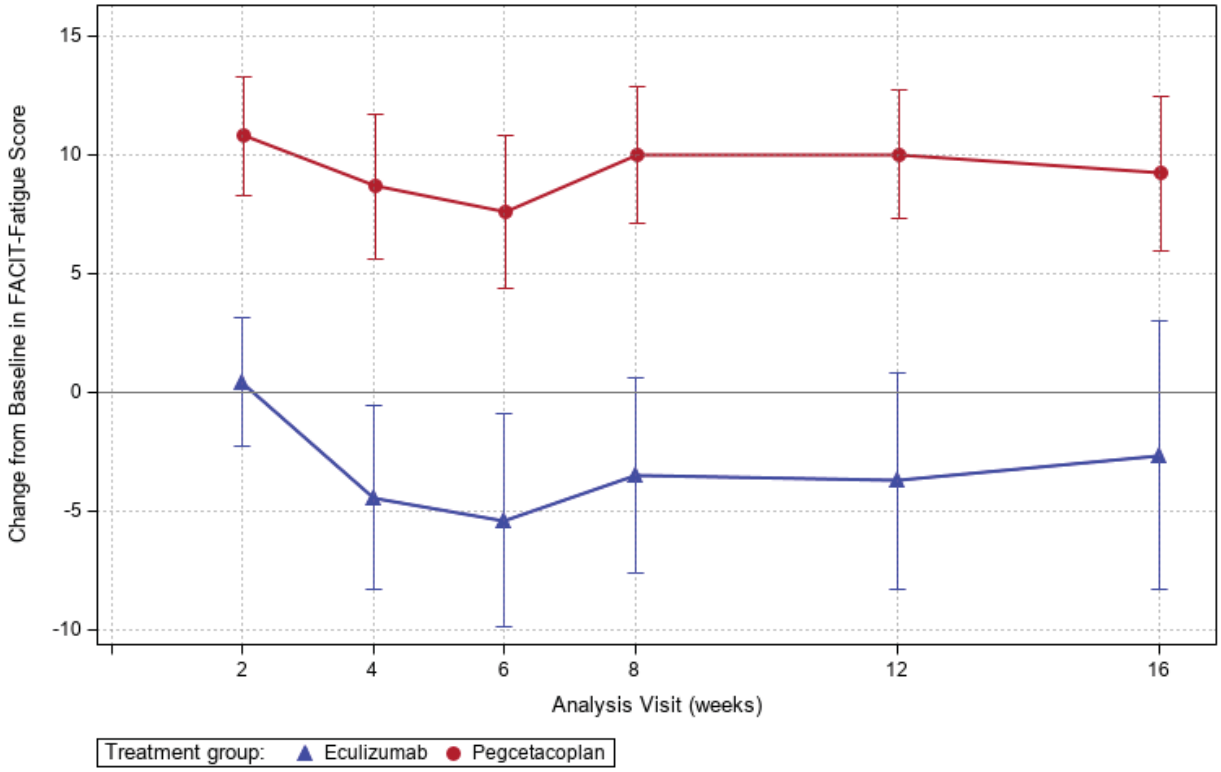
Source: Statistical reviewer's analysis.
Patients (b) (6) with outlier baseline LDH levels of 1598 U/L and 1078.5 U/L were excluded.
[1] Endpoint values after transfusion and study withdrawal were set to missing.
[2] Nominal p-value was based on a mixed model for repeated measures, which included the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.
Two patients with outlier baseline LDH levels were excluded.
Abbreviations: CFB, change from baseline; CI, confidence interval; ITT, intent-to-treat; LDH, lactate dehydrogenase; LSM, least squares mean; N, number of patients; RCP, randomized control period

Table 80. CFB in FACIT-F Score During RCP, ITT Population, APL2-302

Week	Pegcetacoplan 1,080 mg N=41 LSM CFB[1] 95% CI	Eculizumab N=39 LSM CFB[1] 95% CI	Pegcetacoplan and Eculizumab Difference in LSM 95% CI
Week 2	10.79 (8.28, 13.30)	0.45 (-2.27, 3.17)	10.34 (6.90, 13.78)
Week 4	8.69 (5.64, 11.74)	-4.41 (-8.29, -0.53)	13.10 (8.35, 17.84)
Week 6	7.59 (4.38, 10.80)	-5.37 (-9.86, -0.87)	12.95 (7.60, 18.31)
Week 8	10.01 (7.12, 12.89)	-3.49 (-7.60, 0.61)	13.50 (8.67, 18.33)
Week 12	10.02 (7.32, 12.72)	-3.71 (-8.24, 0.81)	13.74 (8.67, 18.80)
Week 16	9.22 (5.96, 12.48)	-2.65 (-8.29, 2.99)	11.87 (5.49, 18.25)

Source: Study APL2-302 Clinical Study Report, Table 33 (p. 121); statistical reviewer's analysis.
[1] Endpoint values after transfusion and study withdrawal were set to missing.
Results are based on a mixed model for repeated measures, which included the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.
Abbreviations: CFB, change from baseline; CI, confidence interval; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; ITT, intent-to-treat; LSM, least squares mean; N, number of patients; RCP, randomized control period

Figure 37. Mean CFB in FACIT-F Score During RCP by Visit and Treatment Group, ITT Population, APL2-302



Note: Treatment effect estimates from a mixed model are shown.
Note: The mixed model contained the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.
Note: Vertical lines represent 95% confidence intervals for least squares mean estimates.

Source: Statistical reviewer's analysis.
Endpoint values after transfusion and study withdrawal were set to missing.
Abbreviations: CFB, change from baseline; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; ITT, intent-to-treat; RCP, randomized control period

16.2. Sensitivity Analyses for Primary Endpoint

Sensitivity analyses were conducted for the primary efficacy endpoint in the intent-to-treat population to examine the departures from the assumptions regarding missing data in the Applicant's prespecified efficacy analysis. The parametric mixed model for repeated measures for the comparison of means was the prespecified analysis method for the primary endpoint and was based on the assumption that data were missing at random.

The statistical reviewer's sensitivity analyses include a pattern mixture model and a tipping point analysis. In the pattern mixture model, missing data from the pegcetacoplan group were imputed under a missing not at random (MNAR) assumption and utilized data from the eculizumab group as a reference. Missing data from the eculizumab group were also imputed under this assumption. The imputation model included the following variables: stratification factors, baseline Hb level, and CFB in Hb level at each time point. Because the number of observations at Week 16 in the eculizumab group was too small to allow for imputation model convergence, missing data at Week 16 were imputed by a method that utilized the group of observations where all the imputation model variables were nonmissing.

In the tipping point analysis, data from both treatment groups were imputed under an MNAR assumption. In this method, missing values in each treatment group were imputed separately using observed values in each group, and an adjustment for each group was applied to the imputed values. The imputation model included stratification factors, baseline Hb level, and CFB in Hb level at each time point. Adjustments for each treatment group were subsequently varied to find conditions that would result in a treatment effect that was not significant. The plausibility of the adjustments that resulted in nonsignificance was then evaluated.

Before sensitivity analyses for the intent-to-treat population were conducted, nonmonotone missing data were first imputed using a missing at random assumption, and monotone missing data were then imputed using a MNAR assumption. Because the missing at random assumption cannot be tested, sensitivity analyses based on the MNAR assumption provide a comprehensive examination of the effect of missing efficacy data. For each sensitivity analysis, 50 datasets with imputed data were created, and analysis results were combined using Rubin's rule.

There were 38 patients with missing Hb data at Week 16 (33 in the eculizumab group, 5 in the pegcetacoplan group); all of those patients received a transfusion during the RCP.

Pattern mixture model results are shown in Table 81. The results are consistent with those of the primary endpoint analysis (Table 12). The difference in least squares means (LSMs) between the treatment groups was 4.66 g/dL (95% CI 0.70 to 8.62, nominal p=0.0219).

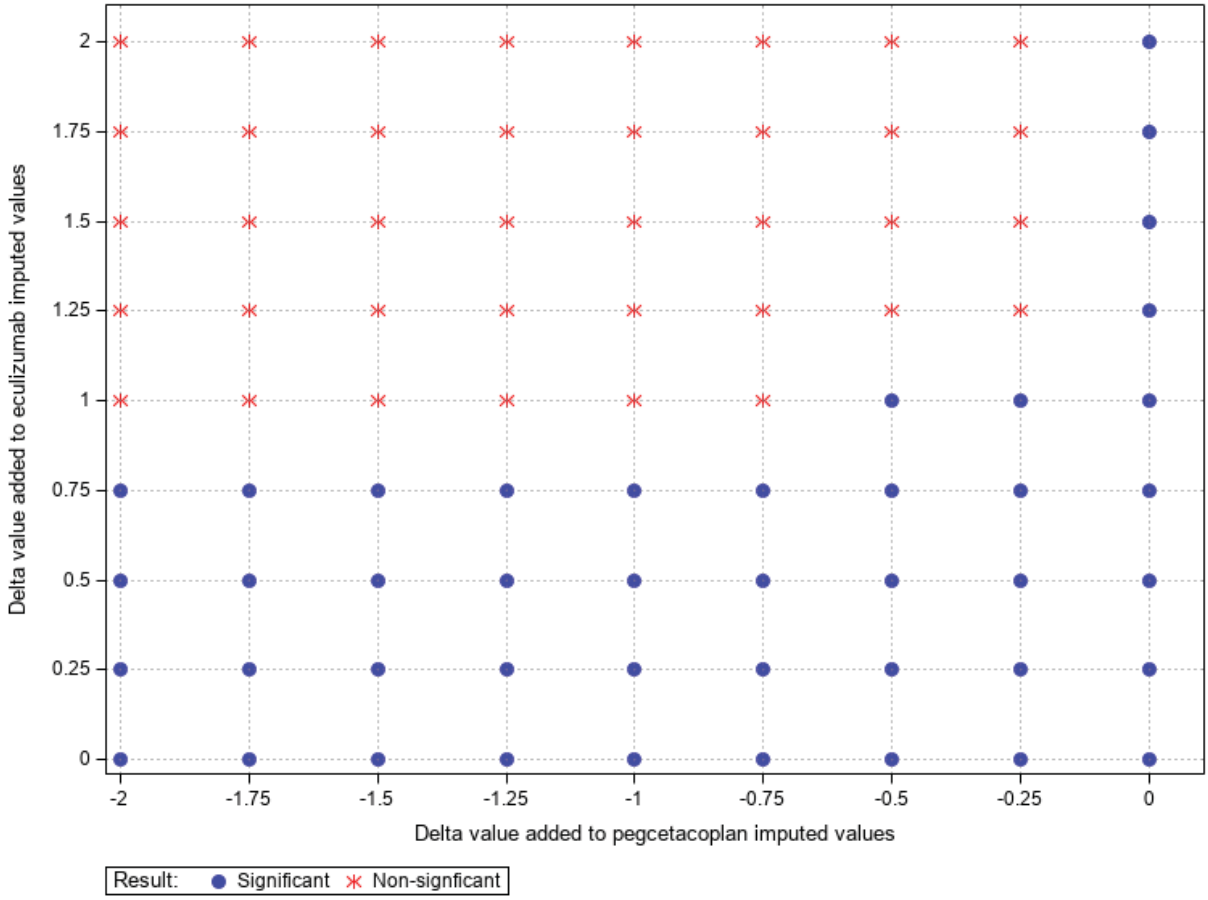
Table 81. Pattern Mixture Model for Mean CFB in Hb Level at Week 16 of RCP, ITT Population, APL2-302

Parameter	Value
LSM CFB in Hb (g/dL) (95% CI)	
Pegcetacoplan 1,080 mg, N=41	2.61 (1.30, 3.92)
Eculizumab, N=39	-2.05 (-5.94, 1.84)
Difference in LSM between pegcetacoplan and eculizumab (95% CI)	4.66 (0.70, 8.62)
Nominal p-value for difference in LSM[1]	0.0219

Source: Statistical reviewer's analysis.
[1] Nominal p-value was based on a mixed model for repeated measures, which included the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.
Abbreviations: CFB, change from baseline; CI, confidence interval; Hb, hemoglobin; ITT, intent-to-treat; LSM, least squares mean; N, number of patients; RCP, randomized control period

Tipping point analysis results are displayed in Figure 38. Adjustments of -0.75, -1, -1.25, and -1.5 to the imputed pegcetacoplan values and +1 to the imputed eculizumab values tipped the resulting p-value for the comparison of LSMs to >0.05. These adjustment values resulted in LSM differences of 1.93, 1.87, 1.82, and 1.76 g/dL, respectively. Other values that tipped the comparison of LSMs p-value are displayed in Figure 38. The assumption that patients with missing data in the two groups would have shown changes with the magnitude of adjustment values in Figure 38 does not seem plausible, given the fact that such changes were observed in few individual patients in the study.

Figure 38. Tipping Point Analysis for Mean CFB in Hb Level at Week 16 of the RCP, ITT Population, APL2-302



Source: Statistical reviewer's analysis.
Abbreviations: CFB, change from baseline; Hb, hemoglobin; ITT, intent-to-treat; RCP, randomized control period

Therefore, despite the occurrence of missing Hb data at Week 16, the aforementioned pattern mixture model and tipping point sensitivity analyses demonstrated that the primary endpoint analysis results were robust to alternate scenarios for missing data assumptions.

In addition, in the prespecified analyses of the primary and continuous key secondary efficacy endpoints, if a patient received a transfusion during the RCP or withdrew from the trial, the endpoint parameter values up to the time of transfusion or withdrawal were used in the analysis model, and subsequent parameter values were assigned as missing. The Applicant performed a supplementary analysis for the primary endpoint in which all available data were utilized in the mixed model. In this analysis, the LSM CFB in Hb at Week 16 in the pegcetacoplan and eculizumab groups was 2.66 g/dL and -0.03 g/dL, respectively (Clinical Study Report, Table 25). The difference in LSMs between the treatment groups was 2.69 g/dL (95% CI 1.99 to 3.38, nominal p<0.0001. These are consistent with the primary endpoint results (Table 12).

16.3. Subgroup Analyses

Table 82 shows exploratory analyses of the primary efficacy endpoint by sex, age, race, and region subgroups. Due to the small numbers of patients in some race categories (Table 8), subgroup analyses by race were conducted for two categories: white and not reported/non-white.

The subgroup analysis results indicate that the pegcetacoplan group achieved at least a ~1.5 g/dL increase in Hb by Week 16, and the eculizumab group had negative LSM CFB values. Model convergence was not reached for the age ≥65 years subgroup and for the Asia-Pacific and North America regions. In general, the subgroup analysis results were consistent with the primary endpoint results (Table 12). These subgroup analyses are limited by the small numbers of patients, and so the results should be interpreted with caution.

Table 82. CFB in Hb Level by Sex, Age, Race, and Region at Week 16 of RCP, ITT Population, APL2-302

Parameter	Value
Sex: female	
LSM CFB in Hb (g/dL)[1] (95% CI)	
Pegcetacoplan 1,080 mg, N=41, n=27	1.64 (0.50, 2.78)
Eculizumab, N=39, n=22	-1.95 (-4.30, 0.40)
Difference in LSM between pegcetacoplan and eculizumab (95% CI)	3.59 (1.00, 6.18)
Sex: male	
LSM CFB in Hb (g/dL)[1] (95% CI)	
Pegcetacoplan 1,080 mg, N=41, n=14	3.87 (2.66, 5.09)
Eculizumab, N=39, n=17	-0.93 (-2.45, 0.58)
Difference in LSM between pegcetacoplan and eculizumab (95% CI)	4.80 (2.89, 6.72)
Age: <65 years	
LSM CFB in Hb (g/dL)[1] (95% CI)	
Pegcetacoplan 1,080 mg, N=41, n=31	2.61 (1.30, 3.92)
Eculizumab, N=39, n=32	-2.05 (-5.94, 1.84)
Difference in LSM between pegcetacoplan and eculizumab (95% CI)	4.66 (0.70, 8.62)
Age: ≥65 years	
LSM CFB in Hb (g/dL)[1] (95% CI)	
Pegcetacoplan 1,080 mg, N=41, n=10	
Eculizumab, N=39, n=7	NA
Difference in LSM between pegcetacoplan and eculizumab (95% CI)	NA
Race: white	
LSM CFB in Hb (g/dL)[1] (95% CI)	
Pegcetacoplan 1,080 mg, N=41, n=24	2.27 (0.88, 3.66)
Eculizumab, N=39, n=25	-2.26 (-4.25, -0.28)
Difference in LSM between pegcetacoplan and eculizumab (95% CI)	4.53 (2.11, 6.96)
Race: not reported or non-white	
LSM CFB in Hb (g/dL)[1] (95% CI)	
Pegcetacoplan 1,080 mg, N=41, n=17	2.00 (0.94, 3.06)
Eculizumab, N=39, n=14	-1.55 (-3.64, 0.53)
Difference in LSM between pegcetacoplan and eculizumab (95% CI)	3.55 (1.24, 5.86)
Region: Europe	
LSM CFB in Hb (g/dL)[1] (95% CI)	
Pegcetacoplan 1,080 mg, N=41, n=25	2.86 (2.07, 3.65)
Eculizumab, N=39, n=19	-0.92 (-2.30, 0.45)
Difference in LSM between pegcetacoplan and eculizumab (95% CI)	3.78 (2.27, 5.30)

Parameter	Value
Region: Asia-Pacific	
LSM CFB in Hb (g/dL)[1] (95% CI)	
Pegcetacoplan 1,080 mg, N=41, n=6	
Eculizumab, N=39, n=12	NA
Difference in LSM between pegcetacoplan and eculizumab (95% CI)	NA
Region: North America	
LSM CFB in Hb (g/dL)[1] (95% CI)	
Pegcetacoplan 1,080 mg, N=41, n=10	
Eculizumab, N=39, n=8	NA
Difference in LSM between pegcetacoplan and eculizumab (95% CI)	NA

Source: Statistical reviewer's analysis.
[1] Endpoint values after transfusion and study withdrawal were set to missing.
Results are based on a mixed model for repeated measures, which included the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.
Abbreviations: CFB, change from baseline; CI, confidence interval; Hb, hemoglobin; ITT, intent-to-treat; LSM, least squares mean; N, number of patients; n, number of patients with specified characteristic; NA, not applicable; RCP, randomized control period

17. Clinical Safety: Additional Information and Assessment

17.1. Analysis of Adverse Events of Special Interest for Supportive Studies

Infections

Infections, all were a common TEAE in the supportive studies. The most common infection reported in all supportive trials was upper respiratory tract infection. There was one TEAE of sepsis; the narrative is provided in Section 18.1.7. There were no reported serious infections with encapsulated bacteria, including meningococcal infections, in the supportive studies. A list of all infections in the primary safety population is shown in Table 83.

Table 83. All Infections in the Primary Safety Population, APL2-202, APL2-204, and CP0514

Infection Type[1]	APL2-202 N=4 n %	APL2-204 Cohort 2 N=20 n %	CP0514 Cohort 4 N=6 n (%)
Infections, all[2]	1 (25)	9 (45)	9 (66.7)
Herpes virus[2]	0 (0)	1 (5)	0 (0)
Viral infection	0 (0)	1 (5)	2 (33.3)
Nasopharyngitis[2]	1 (25)	3 (15)	0 (0)
Upper respiratory tract infection[2]	1 (25)	7 (35)	3 (50)
Abscess[2]	0 (0)	1 (5)	0 (0)
Influenza	0 (0)	0 (0)	2 (33.3)
Sepsis	0 (0)	0 (0)	1 (16.7)
Urinary tract infection	0 (0)	0 (0)	1 (16.7)

Source: Clinical data scientist and FDA clinical reviewer.
[1] Coded as FDA Medical Queries.
[2] The following terms were combined:
Abscess includes nasal abscess
Herpes virus includes: ophthalmic herpes zoster
Infections include: influenza-like illness, nasopharyngitis, rhinitis, cholangitis, acute cholecystitis, hordeolum, nasal abscess, ophthalmic herpes zoster, paronychia, pharyngitis, influenza, sepsis, upper respiratory tract infection, ear infection, urinary tract infection
Nasopharyngitis includes: nasopharyngitis, rhinitis, pharyngitis
Upper respiratory tract infection includes: influenza like illness, nasopharyngitis, rhinitis, pharyngitis, upper respiratory tract infection
Abbreviations: N, number of subjects; n, number of subjects with adverse event

Infections in Ongoing Studies

Per the Applicant, during the open-label phase of Study APL2-302, 42 of 77 patients (54.5%) experienced TEAEs included in the system organ class of infections and infestations. The incidence was similar in the crossover to pegcetacoplan group (21 patients [53.8%]) and the pegcetacoplan continuation group (21 patients [55.3%]). The event of COVID-19 was the only infection TEAE that led to discontinuation due to death. Infections experienced by at least one patient were nasopharyngitis (12 patients [15.6%]), upper respiratory tract infection (8 patients [10.4%]), urinary tract infection (7 patients [9.1%]), oral herpes (5 patients [6.5%]), sinusitis (three patients [3.9%]), respiratory tract infection (2 patients [2.6%]), and rhinitis (2 patients [5.1%]). Four patients experienced sepsis during the open-label phase and follow-up period of Study APL2-302. These events included severe biliary sepsis in one patient in the pegcetacoplan continuation group, postprocedural sepsis in one patient in the crossover to pegcetacoplan group, and two events of severe sepsis (not specified) in one patient in the pegcetacoplan continuation group and one patient in the crossover to pegcetacoplan group during the open-label run-in period. Narratives of these events are provided in Section 18.1.7.

Injection Site Reactions

The TEAE of injection site reaction occurred in 2 of 4 (50%) patients in Study APL2-202 and in 6 of 20 (30%) patients in Cohort 2 of Study APL2-204. In Cohort 4 of Study CP0514, five of six (83.3%) patients experienced an injection site reaction TEAE. This FDA medical query included preferred terms such as injection site erythema, injection site reaction, injection site swelling, injection site bruising, and injection site pain. No injection site reaction was considered to be severe or led to discontinuation of study drug. Most injection site reactions were graded 1 or 2 in severity.

Table 84. Injection Site Reactions in the Supportive Safety Population, APL2-202, APL2-204, and CP0514

Injection Site Reaction[1]	APL2-202 N=4 n %	APL2-204 Cohort 2 N=20 n %	CP0514 Cohort 4 N=6 n (%)
Injection site reaction	2 (50)	6 (30)	5 (83.3)
Injection site erythema	1 (25)	4 (20)	3 (50)
Injection site swelling	1 (25)	1 (5)	2 (33.3)
Injection site induration	0 (0)	1 (5)	2 (33.3)
Injection site bruising	0 (0)	0 (0)	4 (66.7)
Injection site pain	0 (0)	1 (5)	4 (66.7)
Injection site pruritus	1 (25)	0 (0)	1 (16.7)
Administration site swelling	1 (25)	0 (0)	0 (0)
Injection site hemorrhage	0 (0)	0 (0)	1 (16.7)
Injection site edema	0 (0)	0 (0)	1 (16.7)
Injection site warmth	0 (0)	0 (0)	1 (16.7)

Source: Clinical data scientist.
[1] Coded as FDA Medical Queries.
Abbreviations: N, number of subjects; n, number of subjects with adverse event

Injection Site Reactions in Ongoing Studies

The 120-Day safety update included a TEAE of pyrexia for Study APL2-307; the narrative is provided below:

- Subject (b) (6) experienced mild pyrexia (formerly severe fever and empiric meningitis), which led to hospitalization. The patients was admitted to hospital for low grade fever to 99.9°F and abdominal bloating with neck stiffness for 1 week. Patient was admitted to hospital and started on empiric antibiotic coverage for meningitis and Neupogen for neutropenia. Patient received packed RBC transfusion while hospitalized. Blood cultures were negative. CT of the chest, abdomen and pelvis showed ground glass opacities in the lungs with no sign of infection. Antibiotics were discontinued after patient remained afebrile for 72 hr. On Study Day 191, the event term was changed from empiric meningitis to fever. The subject recovered on Day 196. The Applicant assessed the event to be possibly due to pegcetacoplan and investigator thought symptoms were due to viral infection which resolved. Pegcetacoplan was increased due to pyrexia.

In the open-label phase of Study APL2-302, six patients (17.1%) experienced injection site reactions during the run-in period of Weeks 17 to 20. During pegcetacoplan monotherapy, 19 patients (23.3%) experienced injection site reactions, 11 patients (28.2%) in the crossover to pegcetacoplan group and 7 (18.4%) in the pegcetacoplan continuation group. Injection site pruritus was more frequent in the crossover to pegcetacoplan group. No patients discontinued due to injection site reactions. No injection site reactions were severe.

Hemolysis

In Cohort 2 of Study APL2-204, 5 of 20 (25%) patients experienced a TEAE of hemolysis. One event of hemolysis coincided with a fatal SAE of aplastic anemia. Details of this event are provided in Section 6.2. No TEAE of hemolysis was reported in Study APL2-202 or in Cohort 4 of Study CP0514.

Hemolysis in Ongoing Studies

A total of 18 of 77 patients (23.4%) experienced TEAEs in the standardized Medical Dictionary for Regulatory Activities query of hemolytic disorders in the open-label phase of Study APL-302. The incidence was similar in the crossover to pegcetacoplan group (nine patients [23.1%]) and the pegcetacoplan continuation group (nine patients [23.7%]). Hemolysis was reported for 15 patients (19.5%), 8 (20.5%) in the crossover to pegcetacoplan group, and 7 (18.4%) in the pegcetacoplan continuation group. Hemolysis was an SAE for 5 (5.6%) of these 15 patients. Two patients (2.6%) discontinued because of nonserious events of hemolysis. Severe hemolytic anemia was reported in two patients (2.6%) in the pegcetacoplan continuation group and one (2.6%) in the pegcetacoplan continuation group. There was one SAE of hemolytic anemia that led to discontinuation.

Thrombosis

There was one SAE of portal vein thrombosis in Study CP0514 experienced by a patient with a history of deep vein thrombosis in the setting of sepsis. Details of this event are provided in Section 18.1.7. Of note, the patient's last doses of pegcetacoplan and eculizumab prior to the event were administered 1 and 17 days, respectively, before onset of the SAE.

During the open-label phase of Study APL2-302, one subject who had a treatment-related SAE of intestinal ischemia was also diagnosed with Budd–Chiari syndrome.

Thrombosis in Ongoing Studies

Two patients had events of embolism and thrombosis during the open-label phase of Trial APL2-302. One SAE event of deep vein thrombosis occurred in the setting of diffuse large B-cell lymphoma, sepsis, and breakthrough hemolysis. The patient discontinued due to diffuse large B-cell lymphoma. The second event was a moderate AE of jugular vein thrombosis in the setting of pneumonia infection and renal failure. The patient later discontinued due to intestinal ischemia.

Hypersensitivity

Study APL2-204 had one event of serious hypersensitivity in Cohort 1, which was an acute reaction of moderate severity with a close temporal relationship to the start of treatment with pegcetacoplan. A narrative is provided below. Additional generalized reactions such as rash, maculopapular rash, and urticaria were reported and were considered mild or moderate in severity.

- Subject (b) (6) in Cohort 1 (180 mg/day pegcetacoplan) had a moderate SAE of hypersensitivity deemed related to pegcetacoplan by the investigator. The event occurred on Day 1 and led to the patient's discontinuation from the study. The subject was negative for antipegcetacoplan peptide antibody response predose on Day 1. No further monitoring of this subject's antipegcetacoplan peptide antibody response was performed.

Hypersensitivity in Ongoing Studies

A total of 13 of 77 patients (16.9%) experienced TEAEs in the standardized Medical Dictionary for Regulatory Activities query of hypersensitivity. Hypersensitivity events were more frequent

in the crossover to pegcetacoplan group (nine patients [23.1%]) than in the pegcetacoplan continuation group (four patients [10.5%]). The events of allergy to immunoglobulin (one patient [1.3%]) and hypersensitivity pneumonitis (one patient [1.3%]) were also SAEs. Each event was reported in one patient (1.3%), with the exception of acute respiratory failure and erythema which was reported in two patients. One patient (2.6%) in each group experienced severe acute respiratory failure and neither even resulted in discontinuation. One patient in each group experienced erythema.

Baseline Hemoglobin Levels by Study

Table 85 shows the baseline hemoglobin levels at enrollment for Study APL2-302 and supportive Studies APL2-202, APL2-204, and CP0514.

Table 85. Baseline Hemoglobin Levels for Study APL2-302 and Supportive Studies APL2-202, APL2-204, and CP0514

Baseline Hb Level	Statistics	APL2-302		APL2-202	APL2-204	APL-CP0514	Total
		Pegcetacoplan (N=41)	Eculizumab (N=39)	Pegcetacoplan (N=4)	Pegcetacoplan (N=22)	Pegcetacoplan (N=9)	Pegcetacoplan (N=76)
Hb ≤9	n (%)	25 (61.0)	21 (53.8)	4 (100.0)	12 (54.5)	4 (44.4)	45 (59.2)
Hb > 9 to <10	n (%)	11 (26.8)	16 (41.0)	0	3 (13.6)	2 (22.2)	16 (21.1)
Hb ≥ 10	n (%)	5 (12.2)	2 (5.1)	0	7 (31.8)	3 (33.3)	15 (19.7)

Source: Applicant Information Request Response
Abbreviations: Hb, hemoglobin; N, number of subjects; n, number of subjects with indicated baseline Hb

17.2. QT and Immunogenicity Assessment

QT Interval Prolongation

The QT interval effect of pegcetacoplan was evaluated using data from Studies APL2-101 and APL2-302. Based on E-R analysis, pegcetacoplan was not associated with large mean increases (i.e., >20 ms) in the QTc (Table 86). The findings of this analysis are further supported by the available nonclinical data (see the QT IRT review by Dr. Girish Bende in the Document Archiving, Reporting and Regulatory Tracking System on December 2, 2020).

Table 86. Point Estimates and 90% CIs

ECG Parameter	Treatment	Concentration µg/mL	ΔQTcF ms)	90% CI (ms)
QTc	1,080 mg (twice weekly)	595	-0.8	(-3.4 to 1.8)

Source: FDA analysis.
Abbreviations: CI, confidence interval; ECG, electrocardiogram; QTc, corrected QT interval; QTcF, QT interval corrected with Fridericia's formula

Immunogenicity

The immunogenicity of pegcetacoplan was evaluated in 177 patients from Studies APL2-101, APL2-205, APL2-102, APL2-202, APL2-204, and APL2-302 using newly developed ADA assays for anti-pegcetacoplan peptide and anti-PEG antibodies.

Antipegcetacoplan Peptide Antibody

Of 177 subjects, 4 (5%) patients with PNH and 4 (4%) healthy controls had samples with confirmed antipegcetacoplan peptide antibody (Table 87). The percentage of samples confirmed to be positive in these studies was <3.1%. The range of antipegcetacoplan peptide antibody titers for the eight subjects was ≤1:10 and 1:40, which is considered low and unlikely to be clinically relevant. However, as stated under Section 14.4, the ADA assays are subject to interference by onboard pegcetacoplan. Due to the deficiency of these assays, the incidence of anti-pegcetacoplan peptide antibodies may be underestimated.

In Study APL2-302, two patients (Subjects (b) (6)) from the eculizumab group were confirmed to have neutralizing ADA at the end of the randomized control period (16 weeks after discontinuation of pegcetacoplan treatment received from the 4-week run in period). No trend of a reduction in systemic pegcetacoplan exposure was observed in these subjects and the therapeutic effect of pegcetacoplan was maintained during the open-label period when these patients resumed pegcetacoplan treatment after the randomized control period. In addition, ADA tests were negative at the end of the open-label period (Week 48) for both patients. The PK profiles of the two healthy controls positive for neutralizing ADA were similar to others in the same cohort. However, it should be noted that all 4 subjects (2 patients and 2 healthy subjects) with positive anti-pegcetacoplan antibodies only received 4 weeks of pegcetacoplan treatment. Considering the short duration of pegcetacoplan treatment in these subjects and the limited sample size, potential impact of anti-pegcetacoplan peptide antibodies on PK, safety and efficacy of pegcetacoplan cannot be adequately assessed.

Anti-PEG Antibody Response

Of 177 patients, 137 (77.4%) had pre-existing anti-PEG antibody in the predose samples. This is not unusual because PEG is widely used in various products, including medicines, cosmetics, and foods. In Study APL2-302, the incidence of treatment-emergent or treatment-boosted anti-PEG responses was low (one occurrence each; Subjects (b) (6) from the pegcetacoplan group). The treatment-boosted anti-PEG response was transient. Titers associated with the treatment-emergent anti-PEG response and treatment-boosted anti-PEG response were considered low ≤1:40) and unlikely to be clinically relevant.

Table 87.. Summary of Antipegcetacoplan Peptide and Neutralizing Antibody Responses

	Study					
	APL2-302	APL2-204	APL2-202	APL2-101	APL2-205	APL2-102
Parameter	Patients With PNH			Healthy Controls		
Total subjects	80	17	4	40	16	20
Number (%) of subjects positive for ADA	2 (2.5)	2 (11.8)	0 (0)	3 (7.5)	1 (6.3)	0 (0)
Number (%) of subjects positive for NAb	2 (2.5)	0 (0)	NA	2 (5.0)	NA	NA
Total samples analyzed for ADA	486	177	35	166	32	37
Number (%) of samples positive for ADA	2 (0.4)	2 (1.1)	0 (0)	3 (1.8)	1 (3.1)	0 (0)
Titers of ADA	1:10, 1:10,	1:10, 1:10, y	NA	<1:10, 1:10, 1:10,	1:40	NA
Number (%) of samples positive for NAb	2 (0.4)	0 (0)	NA	2 (1.2)	NA	NA

Source: Applicant's amended BA report BAL-19-143-073.
Abbreviations: ADA, antidrug antibodies; NAb, neutralizing antibodies; PNH, paroxysmal nocturnal hemoglobinuria

18. Supportive Studies: Individual Reviews of Supportive Studies For Safety and Efficacy Submitted to the NDA

This section is intended to provide additional data analyses and the clinical review team's interpretation of the more detailed data that helped support the conclusions outlined in Sections 1 and 8.

The supportive studies submitted to this NDA included Study APL2-202, Cohort 2 of Study APL2-204, and Cohort 4 of Study CP0514. The subjects in this supportive analysis included patients who received multiple doses of pegcetacoplan at or near the targeted dose of 1,080 mg.

18.1.1. Study Designs for Supportive Studies APL2-202, APL2-204, and CP0514

Study APL2-202

Study APL2-202 was a Phase 2a, open-label, multiple-dose study in subjects with PNH who had never received eculizumab in the past. A single cohort of subjects was planned for evaluation. Up to 20 subjects were planned to be enrolled to complete 28 days of dosing. Because of enrollment rates and emerging data from ongoing studies, the decision was made to stop enrollment at four subjects. The study consisted of four parts:

- Part 1: Subjects received pegcetacoplan for 28 days.
- Part 2A: After review of available safety, PK, and PD data by the Applicant and investigator, subjects showing evidence of clinical benefit progressed to Part 2A and continued to receive daily doses of pegcetacoplan until Day 84.

- Part 2B: After review of available safety, PK, and PD data by the investigator and Applicant, subjects showing evidence of clinical benefit progressed to Part 2B and continued to receive daily doses of pegcetacoplan until Day 364.
- Part 3: Safety follow-up (up to Day 414) or transition to an open-label extension study.

The planned dosage for this single-cohort study was 270 mg/day; however, from Part 2A onwards intrasubject dose escalation up to a dosage of 360 mg/day was permitted if a subject had a suboptimal clinical response during daily dosage with 270 mg/day pegcetacoplan. All subjects in this study received pegcetacoplan 270 mg/day. All subjects transitioned to the open-label extension study after Day 364.

Four subjects from this trial were included in the supportive safety and efficacy data for this application.

Study APL2-204

Study APL2-204 was a Phase 1b, open-label, multiple ascending dose, pilot study to assess the safety, tolerability, preliminary efficacy, and PK of SC pegcetacoplan in subjects with PNH who had no received prior treatment with eculizumab. Subjects in Cohort 1 received 180 mg/day pegcetacoplan for up to 28 days. Subjects in Cohort 2 received 270 mg/day pegcetacoplan for up to 364 days. Subjects could continue treatment with pegcetacoplan by transitioning to an open-label extension study. In Cohort 2, if clinically indicated on the basis of response, the pegcetacoplan dosage could be increased to 360 mg/day. Cohort 2 was not initiated until all subjects in Cohort 1 had reached the Day-29 visit and the safety monitoring committee had reviewed emerging safety and efficacy data. The study consisted of three parts:

- Part 1 (Days 1 to 28), subjects received pegcetacoplan daily for 28 days. After completion, Cohort 1 subjects proceeded immediately to Cohort 3. Cohort 2 subjects showing evidence of clinical benefit after review of safety, PK, and PD data progressed to Part 2A. Cohort 2 subjects who did not show evidence of clinical benefit proceeded to Part 3.
- Part 2 (Days 29 to 364):
  - Part 2A (Days 29 to 84): Patients continued to receive pegcetacoplan daily until Day 84.
  - Part 2B (Days 85 to 264): Subjects continued to receive pegcetacoplan daily until Day 364. If clinical benefit stopped or there were safety concerns, subjects proceeded to Part 3 immediately. After completion of Part 2B, subjects could continue treatment with pegcetacoplan by transitioning to an open-label extension study or Part 2C if enrollment into the extension study was not yet available. Subjects entering Part 2C continued their pegcetacoplan dose and regimen until enrollment in the open-label extension study was available.
- Part 3 (Days 365 to 414): Pegcetacoplan administration was discontinued, and subjects were followed for up to 50 Days for safety.

Cohort 2 (n=20) was included as supportive safety and efficacy data for this application.

Study CP0514

Study CP0514 was an open-label, prospective, nonrandomized, single and multiple ascending dose study to assess the safety, tolerability, PK, and PD parameters of pegcetacoplan. The study had four cohorts:

- Cohort 1: Pegcetacoplan 25 mg followed by 5 mg/day for 28 days.
- Cohort 2: Pegcetacoplan 50 mg followed by 30 mg/day for 28 days.
- Cohort 3: Pegcetacoplan 180 mg/day for 28 days.
- Cohort 4: Pegcetacoplan 270 mg/day for up to 729 days with a dosage increase to 360 mg/day if clinically indicated.

Cohorts 1 and 2 entered a single-dose phase that consisted of a single dosing day followed by a waiting period of at least 28 days. Both cohorts then entered a 28-day multiple-dose phase. Cohorts 3 and 4 entered directly into the multiple-dose phase (Study Part 1). After the first 28 days of dosing, Cohort 4 entered Study Part 2 (2a, 2b, and 2c) for up to 729 days. Study Part 3 was an 8-week follow-up period. Study Part 3 applied to subjects in Cohorts 1 to 3 who completed the study and subjects in Cohorts 1 to 4 who were withdrawn from the study. Subjects in Cohort 4 who completed the study could enroll in an open-label extension study without completing Study Part 3. Cohort 4 (n=6) was included as supportive safety and efficacy data for this application.

18.1.2. Study Design for Ongoing Studies

After completion of the RCP of Study APL2-302 (end of Week 16), patients continued into a 32-week open-label pegcetacoplan period in which all patients received twice-weekly doses of pegcetacoplan 1,080 mg. Patients 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), patients were offered entry into an open-label extension study. Patients who did not enter the open-label extension study exited the study after two additional safety visits. At the time of data cutoff, 77 patients (39 in the eculizumab group and 38 in the pegcetacoplan group from the RCP) were enrolled in the ongoing open-label phase.

Study APL2-307 is an open-label, nonrandomized, multicenter extension study evaluating the long-term safety and efficacy of pegcetacoplan. Patients who have completed other pegcetacoplan PNH clinical trials will be eligible to participate in this trial. Planned enrollment is 160 subjects with a duration of 4 years or until the development program for pegcetacoplan in patients with PNH is terminated.

Study APL2-308 is a randomized, multicenter, open-label, controlled study evaluating the efficacy and safety of pegcetacoplan in patients with PNH compared to standard of care (excluding complement inhibitors). The study consists of three periods: A screening period of up to 4 weeks, an RCP of up to 26 weeks, and an 8-week safety follow-up. Patients must not have received treatment with a complement inhibitor for at least 3 months prior to screening. Planned number of subjects is 54 randomized (36 in the pegcetacoplan group and 18 in the standard-of-care group). At the time of data cutoff, this study was ongoing.

18.1.3. Efficacy Findings from Supportive Studies APL2-202, APL2-204, and CP0514

Key efficacy findings for supportive studies APL2-202, APL2-204, and CP0514 are summarized in Table 87. Patients in the three supportive studies showed increases from baseline in hemoglobin level. The mean hemoglobin level at Week 16 (Day 113) ranged from 10.8 g/dL to 12.6 g/dL.

Table 86. Hemoglobin Absolute Value and Change From Baseline by Visit, APL2-202, APL2-204, and CP0514

Hemoglobin (g/dL) Time Point	APL2-202 N=4	APL2-204 Cohort 2 N=20	CP0514 Cohort 4 N=6
Baseline			
mean (SD)	7.7 (0.9)	8.4 (1.8)	8.8 (1.4)
Day 15, n	4	19	6
Mean (SD)	9.6 (1.1)	10.2 (2)	9.7 (1.4)
Mean CFB (SD)	1.7 (0.6)	1.9 (1.4)	0.9 (0.5)
Day 29, n	4	20	6
Mean (SD)	10.3 (1)	11.1 (2)	11.5 (1.7)
Mean CFB (SD)	2.6 (1)	2.8 (2)	2.7 (1)
Day 57, n	4	17	6
Mean (SD)	12 (1.2)	11.8 (2)	11.5 (1.5)
Mean CFB (SD)	4.3 (0.5)	3.6 (2.2)	2.7 (1.8)
Day 85, n	4	17	6
Mean (SD)	12 (1.2)	12 (2.2)	11.8 (1.5)
Mean CFB (SD)	4.3 (0.5)	3.5 (2.3)	3 (1.1)
Day 113, n	4	18	6
Mean (SD)	12.6 (1.4)	11.9 (2.2)	10.8 (1.9)
Mean CFB (SD)	4.9 (0.8)	3.5 (2.3)	2 (1.8)
Day 141, n	4	18	5
Mean (SD)	12.7 (1.5)	12.1 (2.5)	11.8 (0.9)
Mean CFB (SD)	5 (1.2)	3.7 (2.5)	2.7 (1.8)
Day 365, n	4	17	3
Mean (SD)	13 (2.2)	12.1 (2)	12 (1.8)
Mean CFB (SD)	5.3 (1.9)	3.7 (2.7)	2.6 (1.6)
Day 729, n	NA	NA	3
Mean (SD)			11.5 (0.5)
Mean CFB (SD)			2.6 (1.9)

Source: Applicant's Summary of Clinical Efficacy.
Abbreviations: CFB, change from baseline; N, number of patients; n, number of patients at specified time; NA, not applicable

Table 88 displays the secondary efficacy parameter results for the three supportive trials, which are consistent with the findings of Study APL2-302. At least 65% of patients in the supportive trials achieved transfusion avoidance with pegcetacoplan treatment. Absolute reticulocyte count (ARC) reduction was observed in the three supportive trials with a mean CFB at Week 16 of -93.1 to -149.3. Although LDH did not meet noninferiority criteria in Study APL2-302, a reduction in LDH was observed in all three supportive trials with a mean CFB at Week 16 ranging from -2136.2 U/L to -69.8 U/L.

Table 87. Summary of Efficacy Parameters, APL2-202, APL2-204, and CP0514

Parameter	APL2-202 N=4	APL2-204 Cohort 2 N=20	CP0514 Cohort 4 N=6
Hemoglobin, g/dL			
Baseline, mean (SD)	7.7 (0.9)	8.4 (1.8)	8.8 (1.4)
Day 113 (Week 16), n	4	19	6
Mean (SD)	9.6 (1.1)	10.2 (2)	9.7 (1.4)
Mean CFB (SD)	1.7 (0.6)	1.9 (1.4)	0.9 (0.5)
Transfusions, number of transfusions in the 12 months prior to screening			
Baseline, mean (SD)	4.5 (2.4)	5.3 (4.70	5.3 (4.1)
Transfusion avoidance, n (%)	4 (100)	13 (65)	4 (66.7)
ARC, $\times 10^9$/L			
Baseline, mean (SD)	238.3 (91)	194.9 (62.2)	333.9 (121.2)
Day 113 (Week 16), n	4	18	6
Mean (SD)	89 (16.3)	105.1 (42.1)	186.7 (170.6)
Mean CFB (SD)	-149.3 (94.8)	-93.1 (85)	-147.2 (125.7)
LDH, U/L			
Baseline, mean (SD)	2548.8 (631.1)	2388.8 (1014.1)	280.2 (131.1)
Day 113 (Week 16), n	4	18	6
Mean (SD)	243.3 (39.7)	245.8 (99.1)	210.3 (58.7)
Mean CFB (SD)	-2305.5 (633.1)	-2136.2 (1054)	-69.8 (117.8)

Source: Applicant's Summary of Clinical Efficacy.
Abbreviations: ARC, absolute reticulocyte count; CFB, change from baseline; LDH, lactate dehydrogenase

Efficacy was observed over a 16-week timeframe in Study APL2-302. The three supportive studies were longer in duration and support the durability of response to pegcetacoplan for up to 1 year in Study APL2-202 and Study APL2-204 and for approximately 2 years in Study CP0514. Table 89 shows the efficacy results at Day 365 and Day 729 for the three supportive trials.

Table 88. Summary of Efficacy Results at Days 365 and 729, APL2-202, APL2-204, and CP0514

	Hemoglobin, g/dL			ARC, $\times 10^9$/L			LDH, U/L		
Study	**APL2-202**	**APL2-204**	**CP0514**	**APL2-202**	**APL2-204**	**CP0514**	**APL2-202**	**APL2-204**	**CP0514**
Baseline, Mean	7.7	8.4	8.8	238.3	194.9	333.9	2548.8	2388	
(SD)	(0.9)	(1.8)	(1.4)	(91)	(62.2)	(121.2)	(631.1)	(1014.1)	280.2 (131.1)
Day 365, n	4	17	3	4	17	2	4	17	3
Mean	13	12.1	12	94	96.4	74.6	226	306.5	157.7
(SD)	(2.2)	(2)	(0.7)	(26.9)	(33.4)	(13)	(27)	(324.7)	(14.8)
Mean CFB	5.3	3.7	2.5	-144.3	-105.9	-254.5	-2322.8	-2105.2	-54
(SD)	(1.9)	(2.7)	(1.7)	(98.5)	(70.3)	(24.2)	(635.4)	(1078.8)	(27.6)
Day 729, n	NA	NA	3	NA	NA	3	NA	NA	4
Mean			11.5			82.7			249
(SD)			(0.5)			(31)			(89.5)
Mean CFB			2.6			-239.4			39.3
(SD)			(1.9)			(49)			(98.5)

Source: Applicant's Summary of Clinical Efficacy.
Abbreviations: ARC, absolute reticulocyte count; CFB, change from baseline; LDH, lactate dehydrogenase; SD, standard deviation

18.1.4. Efficacy Findings for Ongoing Study, APL2-302 Open-Label Phase

The open-label phase of Study APL2-302 was ongoing as of the data cutoff. Based on the 48-week summary report provided by the Applicant, 77 subjects entered the open-label phase (39 in the eculizumab group and 38 in the pegcetacoplan group from the RCP). Sixty-seven subjects completed treatment.

Per the Applicant, at the start of the open-label period, patients receiving eculizumab monotherapy during the RCP (crossover to pegcetacoplan group) showed a decrease in hemoglobin from baseline at Week 17 (CFB [standard deviation, SD] -0.07 [0.95] g/dL). With the addition of pegcetacoplan treatment at Week 17, patients in the crossover to pegcetacoplan group showed improvement in hemoglobin at Week 18 (CFB [SD] 1.5 [0.96] g/dL), which was sustained at Week 48 (CFB [SD] 3.5 [1.6] g/dL). Patients in the pegcetacoplan continuation group demonstrated sustained improvement in hemoglobin up to Week 48 (CFB [SD] 2.74 [1.7] g/dL). At Week 48, hemoglobin values were comparable between the two groups. In the total pegcetacoplan monotherapy group, the mean CFB in hemoglobin level at Week 48 was 3.1 g/dL when censored for intercurrent events and 2.7 g/dL when all available data were considered.

Fifty-five of seventy-seven (71.4%) patients in the total pegcetacoplan monotherapy group achieved transfusion avoidance and did not require transfusions, comprising 24 of 39 patients (61.5%) in the crossover to pegcetacoplan group and 31 of 38 (81.6%) in the pegcetacoplan continuation group. When analyzed by number of PRBC transfusions in the 12 months prior to Day -28, at Week 48, the number and percentage of subjects with transfusion avoidance in the ≥4 PRBC transfusion stratum were lower than in the <4 PRBC transfusion stratum.

At the start of the open-label phase of Study APL2-302, patients receiving eculizumab monotherapy during the RCP (crossover to pegcetacoplan group) showed an improvement in ARC from baseline at Week 17 (CFB [SD] -7.8 [60.9] 10^9/L). With the addition of pegcetacoplan treatment at Week 17, patients in the crossover to pegcetacoplan group showed additional decreases in ARC as early as Week 18 (CFB [SD] -103.8 [58.8]$\times 10^9$/L), which were sustained at Week 48 (CFB [SD] -140.9 [72.2]$\times 10^9$/L). At Week 48, the improvement in ARC was comparable between groups. Overall, mean CFB in ARC was -133.7$\times 10^9$/L (censored for intercurrent events) and -135.3$\times 10^9$/L (all available data).

The mean CFB (SD) at Week 48 for LDH were comparable for the pegcetacoplan continuation group of -28.7 (154.9) U/L, and the mean CFB (SD) for the crossover to pegcetacoplan group was -44.2 (159.5) U/L.

18.1.5. Safety Findings From Supportive Studies APL2-202, APL2-204, and CP0514

Table 89. Overview of Treatment-Emergent Adverse Events,[1] Controlled Trial Safety Population, APL2-202, APL2-204, and CP0514

Adverse Event	APL2-202 N=4 n (%)	APL2-204 Cohort 2 N=20 n (%)	CP0514 Cohort 4 N=6 n (%)
Any treatment-emergent AE	3 (7.5)	18 (90)	6 (100)
Moderate or severe AEs (grade 3-4)	1 (25)	7 (35)	4 (66.7)
SAEs	1 (25)	6 (30)	2 (33.3)
SAEs with fatal outcome	0 (0)	0 (0)	0 (0)
AEs leading to discontinuation of study drug	0 (0)	2 (10)	0 (0)
AEs leading to dosage modification of study drug	0 (0)	2 (10)	2 (33.3)
AEs leading to interruption of study drug	0 (0)	2 (10)	2 (33.3)
AEs leading to reduction of study drug	0 (0)	0 (0)	0 (0)
AEs leading to dosage delay of study drug	0 (0)	0 (0)	0 (0)

Source: adae.xpt; software: Python.
[1] Treatment-emergent adverse events defined as 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. If more than one AE with the same PT was reported before the date of the first dose, then the AE with the greatest severity was presented in summaries. An AE that occurred more than 30 Days after the date of the last dose was not counted as a TEAE.
Grading scale: Mild, moderate, and severe; Studies APL2-202, APL2-CP-PNH-204, and CP0514: NCI-CTCAE version 4.03.
Studies APL2-202 and APL2-CP-PNH-204 Cohort 2 durations were up to 365 days. Dosage could be increased to 360 mg/day if clinically indicated. Subjects were naïve to C5 inhibitor treatment.
Study CP0514 duration was 2 years. Dosage could be increased to 360 mg/day if clinically indicated. Subjects remained anemic despite treatment with ECU.
Abbreviations: AE, adverse event; N, number of subjects in treatment group; n, number of subjects specified event; NCI-CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Event; PT, preferred term; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Patients in Study APL2-204 experienced more treatment-emergent adverse events (TEAEs) (18/20 or 90%) and SAEs (6/20 or 30%) compared with those in the supportive Studies APL2-202 and CP0514. Two of twenty (10%) subjects in APL2-204 had an adverse event (AE) leading to discontinuation of study drug, compared to zero subjects in APL2-202 and CP0514.

18.1.6. Significant Adverse Events

During Study APL-202, there was one TEAE with grade ≥3 in severity. One patient experienced a rib fracture. During Study APL2-204 in Cohort 2, the most common grade ≥3 TEAEs for patients receiving pegcetacoplan or eculizumab were hemolysis and leukopenia. One subject developed an abdominal neoplasm, which is discussed below as an SAE. In Study CP0514, in Cohort 4, the most common grade ≥3 TEAE was related to liver function test abnormalities. The most common TEAEs of grade ≥3 occurring in the supportive trials are listed in Table 91. Grading was based on the National Cancer Institute–Common Terminology Criteria for Adverse Event.

Table 90. Most Common TEAEs Grade ≥3, Safety Population, APL2-202, APL2-204, and CP0514

Adverse Event[1]	APL2-202 N=4 n %	APL2-204 Cohort 2 N=20 n %	CP0514 Cohort 4 N=6 n (%)
Infection, all[2]	0 (0)	1 (5)	1 (16.7)
Sepsis	0 (0)	0 (0)	1 (16.7)
Acute cholecystitis	0 (0)	1 (5)	0 (0)
Pancreatitis	0 (0)	0 (0)	1 (16.7)
Hyperbilirubinemia	0 (0)	0 (0)	1 (16.7)
Thrombocytopenia	0 (0)	1 (5)	0 (0)
Leukopenia[2]	0 (0)	3 (15)	1 (16.7)
Fracture[2]	1 (25)	0 (0)	0 (0)
Acute kidney injury	0(0)	2 (10)	0 (0)
Hematuria	0 (0)	1 (5)	0 (0)
Portal vein thrombosis	0 (0)	0 (0)	1 (16.7)
Hypocalcemia	0 (0)	1 (5)	0 (0)
Hypokalemia	0 (0)	2 (10)	0 (0)
Blood glucose increased	0 (0)	0 (0)	1 (16.7)
Hypotension	0 (0)	1 (5)	0 (0)
QT prolonged	0 (0)	1 (5)	0 (0)
Aplastic anemia	0 (0)	1 (5)	0 (0)
Hemolysis[2]	0 (0)	3 (15)	0 (0)
Anemia[2]	0 (0)	2 (10)	1 (16.7)
Abdominal neoplasm	0 (0)	1 (5)	0 (0)
Got, gpt, ggtp, lfts[2]	0 (0)	0 (0)	2 (33.3)
Headache	0 (0)	0 (0)	1 (16.7)
Paresthesia[2]	0 (0)	0 (0)	1 (16.7)
Injection site reaction[2]	0 (0)	0 (0)	1(16.7)
Pruritus[2]	0 (0)	0 (0)	1 (16.7)
Pyrexia[2]	0 (0)	1 (5)	1 (16.7)

Source: Clinical data scientist and FDA clinical reviewer.
[1] Coded as FDA medical queries
[2] The following terms were combined:
Anemia includes hemolytic anemia, anemia
Fracture includes rib fracture
Got, gpt, ggtp, lfts includes alanine aminotransferase increased, aspartate aminotransferase increased
Hemolysis includes hemolysis, hemolytic anemia, intravascular hemolysis
Infection, all includes acute cholecystitis, sepsis
Injection site reaction includes injection site pain, injection site pruritus
Leukopenia includes neutropenia, febrile neutropenia, neutrophil count decreased, white blood cell count decreased
Paresthesia includes burning sensation
Pruritus includes injection site pruritus, pruritus
Pyrexia includes febrile neutropenia, pyrexia
Abbreviations: N, number of subjects in group; n, number of subjects with specified event; QT, QT interval; TEAE, treatment-emergent adverse event

18.1.7. Serious Adverse Events, APL2-202, APL2-204, and CP0514

An SAE was reported in one of four (25%) patients in Study APL2-202.

- Subject (b) (6): A 47-year-old female who experienced a severe rib fracture after a motor vehicle accident that resulted in hospitalization. No treatment changes were made due to the event of rib fracture.

In Cohort 2 of Study APL2-204, in addition to the one on-study death and one poststudy death discussed in Section 6.2, SAEs were reported in six subjects during the study. The most common SAE reported was hemolysis, which occurred in 3 of 20 (15%) subjects. Narratives are provided below for the SAEs of hypersensitivity and abdominal neoplasm:

- Subject (b) (6): A 61-year-old female with a history of basal cell carcinoma, papilloma excision, and cold-type hemolytic anemia experienced an intra-abdominal malignancy that resulted in hospitalization and death. Concomitant medications included warfarin. On Day 231 of the study, patient received a dose of pegcetacoplan 360 mg daily and was later admitted to hospital for abdominal distension and pain in the setting of 4 weeks of fatigue and abdominal tenderness and bleeding. Abdominal computed tomography (CT) showed ascites of sigmoid colon and ovarian, pelvic, and mesenteric lesions. Further testing confirmed diagnosis of ovarian adenocarcinoma. Over the next 2 months, the patient was admitted to hospital for pleural effusions and began chemotherapy. Patient discontinued from the study after completion of second cycle of chemotherapy. After study conclusion, patient died of ovarian adenocarcinoma approximately 1 month after study discontinuation. The Applicant concluded that this event did not qualify as an on-study death and therefore is not included in the clinical database.
- Subject (b) (6): A 30-year-old male who experienced a hypersensitivity reaction that resulted in hospitalization. On Day 1 of the study, patient received a single 180 mg SC dose (first dose) of pegcetacoplan. Approximately 3 hr later, the patient reported throat tightness, generalized itchiness, jaw soreness, sweating and facial swelling. He also reported nausea and two episodes of emesis. On examination, the patient had a diffuse maculopapular rash and complained of unusual sensation while swallowing. Patient was admitted for observation. Treatment included IV fluids, loratadine, codeine, metoclopramide, domperidone (after a dystonic reaction to metoclopramide), ondansetron, and paracetamol, and two units of packed RBCs for hemolytic anemia due to PNH. Patient was discharged on study Day 2 with oral amoxicillin for infection prophylaxis. The event was considered resolved on Day 5. Immunological review was conducted and it was summarized that the SAE was not consistent with an immunoglobulin E-mediated reaction or immunoglobulin G-mediated reaction. Enzyme-linked immunosorbent assay testing did not show interleukin-2 or interferon cytokine production. An antidrug antibody enzyme-linked immunosorbent assay showed transient presence of antipegcetacoplan immunoglobulin G antibody in serum for <5 hr following administration of pegcetacoplan. The Applicant deemed this unlikely to be of clinical significance. Overall, the Applicant considered there to be no evidence of drug-induced T-cell activation. The patient withdrew consent for personal reasons and received no further pegcetacoplan.

In Study CP0514, in addition to the one on-study death in Cohort 1, discussed in Section 6.2, two subjects experienced an SAE. The SAEs included portal vein thrombosis, sepsis, ALT and AST increased, anemia, and lower gastrointestinal hemorrhage.

- Subject (b) (6): A 35-year-old randomized to SC injection of 270 mg pegcetacoplan experienced an SAE of lower gastrointestinal hemorrhage of moderate intensity. Patient had a history of aplastic anemia, hematuria, and multiple sclerosis. On Day 39, patient received a dose of pegcetacoplan and later reported bloody stool, bright red in color after bowel movement. The subject had a history of constipation. On examination, patient noted to have a small, external hemorrhoid. Hemoglobin was 9.2 g/dL. Patient was admitted to hospital. On Day 40, laboratory values were stable. A colonoscopy was performed and no blood was seen. Rectal bleeding thought to be secondary to hemorrhoidal bleeding. Subject was discharged home. No changes were made to pegcetacoplan administration.

  On Day 199, the patient received SC injection of pegcetacoplan 360 mg. That same day, the patient was admitted to a local hospital for a planned left staghorn calculus removal with cystoscopy and left percutaneous nephrostomy tube placement. After tube placement, the subject experienced sinus tachycardia and fever to 102°F. The subject was transferred to the intensive care unit for further observation. A chest X-ray was negative. Electrocardiogram (ECG) and cardiac enzymes were not concerning. Patient's hemoglobin level was 6 g/dL and received packed red blood cell transfusion. The subject was administered IV antibiotics. Blood culture tested positive for enterobacteria and *E. coli*. Antibiotic coverage was changed due to fever on Day 202. Patient was discharged on Day 201. No changes were made to pegcetacoplan.

  On Day 207, patient experienced weakness and altered mental status. Patient was taken to hospital and found to be in renal failure with elevated serum creatinine level and liver failure with marked transaminitis. Patient also found to be hypothermic and pancytopenic and subsequently hospitalized. An ultrasound of the liver showed portal vein thrombus and CT revealed a left staghorn calculus with no abscess. The patient was treated with enoxaparin and vitamin K and transfused packed RBCs. During hospitalization, patient experienced vaginal bleeding thought due to anticoagulation therapy, required multiple units of packed RBCs for ongoing anemia and renal stone was removed. On Day 229, patient was discharged and patient's mental status returned to normal. During hospitalization, patient missed one daily dose of pegcetacoplan.

- Subject (b) (6): A 38-year-old female who experienced two SAEs of increased ALT and anemia. Past medical history included acute renal failure, history of ALT and alkaline phosphatase increase. Concomitant medication included fluconazole, ibuprofen, and penicillin V. Prior to patient's entry to Cohort 4, she was on 1200 mg SC eculizumab every 14 days. On Day 28, patient received a 270 mg SC injection of pegcetacoplan. The same day, local laboratory tests indicated increased liver enzymes in the setting of right upper quadrant abdominal pain. This included an ALT of 483 U/L, AST of 159 U/L, and alkaline phosphatase of 251 U/L. Dosing of pegcetacoplan was ceased temporarily. Repeat laboratory testing on Day 29 showed downtrending liver enzymes and enzymes normalized on Day 32. On Day 48, patient experienced a second SAE of anemia to 7.1 g/dL attributed to hemolysis. Laboratory testing also indicated ALT 73 U/L, AST 26 U/L, and alkaline phosphatase 146 U/L. Laboratory values normalized on Day 50.

Consultation with a hepatology expert indicated that elevated liver enzymes were indicative of liver irritation, possibly due to pegcetacoplan.

The SAEs that occurred in the supportive trials are shown in Table 92.

Table 91. Serious Adverse Events, Safety Population, APL2-202, APL2-204, and CP0514

Adverse Event[1]	APL2-202 N=4 n (%)	APL2-204 Cohort 2 N=20 n (%)	CP0514 Cohort 4 N=6 n (%)
Infection, all[2]	0 (0)	1 (5)	1 (16.7)
Acute cholecystitis	0 (0)	1 (5)	0 (0)
Sepsis	0 (0)	0 (0)	1 (16.7)
Fracture[2]	1 (25)	0 (0)	0 (0)
Acute kidney injury	0 (0)	1 (5)	0 (0)
Pneumonitis	0 (0)	1 (5)	0 (0)
Aplastic anemia	0 (0)	1 (5)	0 (0)
Abdominal neoplasm	0 (0)	1 (5)	0 (0)
Lower gastrointestinal hemorrhage	0 (0)	0 (0)	1 (16.7)
Pancreatitis	0 (0)	0 (0)	1 (16.7)
Portal vein thrombosis	0 (0)	0 (0)	1 (16.7)
Hemolysis[2]	0 (0)	3 (15)	0 (0)
Abdominal pain	0 (0)	1 (5)	0 (0)
Got, gpt, ggtp, lfts[2]	0 (0)	0 (0)	1 (16.7)
Anemia	0 (0)	0 (0)	1 (16.7)

Source: Clinical data scientist and FDA clinical reviewer.
[1] Coded as FDA medical queries
[2] The following terms were combined:
Fracture includes rib fracture
Got, gpt, ggtp, lfts includes alanine aminotransferase increased, aspartate aminotransferase increased
Hemolysis includes hemolysis, intravascular hemolysis
Infection, all includes acute cholecystitis, sepsis
Abbreviations: N, number of subjects in group; n, number of subjects with specified event

18.1.8. Significant Adverse Events From Ongoing PNH Studies

During the open-label phase of Study APL2-302, 18 (23.3%) of 77 patients had SAEs. The incidence of SAEs was similar between the crossover to pegcetacoplan group (10 patients [25.6%]) and the pegcetacoplan continuation group (8 patients [21.1%]). Each SAE was reported by one patient, with the exception of hemolysis and gastroenteritis. Hemolysis was reported for five patients (6.5%), three (7.7%) in the crossover to pegcetacoplan group and two (5.3%) in the pegcetacoplan continuation group; two events resulted in discontinuation by two subjects. These SAEs included hemolytic anemia, intestinal ischemia (reported with intrahepatic Budd–Chiari syndrome), biliary sepsis, sepsis, facial paralysis, intestinal obstruction and acute myeloid leukemia, and hypersensitivity pneumonitis. These events were not included in the Study APL2-302 Clinical Study Report because they occurred after Week 16.

The most common SAEs reported were hemolysis (eight patients), abdominal pain (three patients), gastroenteritis (three patients), and sepsis (three patients). Other SAEs included cytopenia (one patient), coronavirus disease-2019 ([COVID-19], one patient), hematoma muscle (one patient), diverticulitis (one patient), thrombocytopenia (one patient), ileal obstruction (one patient), diffuse B-cell lymphoma (one patient), and deep vein thrombosis (one patient). Narratives for fatal or treatment-related SAEs are provided below:

- Subject [redacted]: A 78-year-old male who experienced severe hypersensitivity pneumonitis, formerly chest infection, fever, hospitalization that resulted in hospitalization and was life-threatening. Medical history included PNH and hypothyroidism. Relevant concomitant medication included fluindione for prophylaxis for history of hepatic thrombosis. The subject was randomized to the eculizumab treatment group in [redacted] and transitioned to pegcetacoplan during the open-label phase of the study. In [redacted], patient experienced fever of 38°C without night sweats and was restarted on pegcetacoplan. On [redacted], patient received the most recent dose of eculizumab prior to hospitalization. On [redacted], patient initiated treatment with oral prednisone. In [redacted], patient developed fever to 40°C with dry cough, pleuritic chest pain, and progressive dyspnea on exertion. Patient started on augmentin and received a dose of pegcetacoplan 4 Days prior to hospitalization.

  Patient was hospitalized on [redacted] with CT revealing chronic right frontal sinus disease and diffuse interstitial lung disease with bilateral areas of ground glass appearance. Bronchoalveolar lavage was negative. Infectious work-up was negative. There was no evidence of ongoing hemolysis per investigator. Pegcetacoplan was discontinued on [redacted] and subsequently, a marked improvement was found in respiratory status. Patient started on eculizumab therapy. Pulmonary biopsy on [redacted] revealed interstitial pulmonary fibrosis with recent confluence in alveolar spaces with inflammatory infiltrate consisting mainly of lymphocytes, plasma cells with some granulomas, and epithelioid cells without necrosis. The findings were thought to be consistent with hypersensitivity pneumonitis of noninfectious origin. Patient was discharged afebrile with improvement in breathing. Repeat chest CT revelated improvement in lesions. Patient continued prednisone daily and eculizumab therapy. The investigator and Applicant assessed the event of hypersensitivity pneumonitis as related to pegcetacoplan and not related to eculizumab. The subject discontinued pegcetacoplan treatment and from the study due to this SAE.

- Subject [redacted]: A 33-year-old female who developed a severe treatment-related SAE of hemolytic anemia that resulted in hospitalization and severe multiple splenic infarct. Relevant medical history includes anemia and Budd–Chiari syndrome. Concomitant medication included fluindione. The subject was receiving eculizumab every 15 Days prior to study enrollment. The subject was randomized to the eculizumab group. On [redacted], the open-label treatment started with pegcetacoplan BIW.

  On [redacted], patient presented with fever, abdominal pain, and hemoglobinuria for 1 day. Hemoglobin decreased by 3 g/dL from prior and patient was admitted. All bacterial and viral studies were negative. Patient treated with anti-vitamin K. Patient started on empiric antibiotics. Dosage of pegcetacoplan was increased to three times weekly on [redacted]. On [redacted], the patient experienced intense abdominal pain with dyspnea and hypoxia leading to intensive care unit admission. Patient noted to have anemia, thrombocytopenia, elevated ferritin. CT scan revealed multiple splenic infarcts, possibly related to hemolysis. The prophylactic anticoagulation was withdrawn until platelet count was higher and patient was started on steroids and antibiotic coverage was broadened. Bone marrow examination received hemophagocytosis and the patient was diagnosed with macrophagic activation syndrome. Patient's condition improved with treatment with corticosteroids and reintroduction of eculizumab. The event resolved

20 days after onset. The subject discontinued study drug and the study due to this SAE. Reported events were assessed by the investigator as possibly related to pegcetacoplan.

- Subject (b) (6): A 35-year-old male who experienced severe mesenteric ischemia and postprocedural sepsis that led to hospitalization, was life-threatening, and resulted in significant disability. Medical history anemia and iron overload. Concomitant medications included tinzaparin sodium, meropenem, amikacin, heparin calcium, vancomycin, and gentamycin. Patient was randomized to the eculizumab treatment group and transitioned to pegcetacoplan during the open-label phase of the trial. On (b) (6) (b) (6) (Study Day 71), the patient presented to the emergency department with abdominal spasm and was admitted for treatment. Abdominal ultrasound revealed gallbladder edema, biliary sludge and gallstones without cholecystitis. Patient was discharged home with improvement in pain. Due to continued pain, the patient underwent endoscopic cholecystectomy to remove the gallstone and a prosthesis was placed on Day 77.

  On Day 149, patient was hospitalized and underwent preplanned cholecystectomy. Patient subsequently developed fever and abdominal pain and started on IV antibiotics. CT revealed biliary obstruction. Patient continued on pegcetacoplan on Day 149. On Day 149, the subject was hospitalized for a preplanned cholecystectomy. During hospitalization, the patient experienced postprocedural sepsis and started on unfractionated heparin. During hospitalization, pegcetacoplan treatment was increased to every third day. During hospitalization, the patient developed grade-3 breakthrough hemolysis secondary to sepsis followed by grade-4 kidney failure requiring hemodialysis. The patient developed a bilateral jugular thrombosis attributed to dialysis catheter, and curative heparin was started.

  On (b) (6) patient developed severe hepatic enzyme cytolysis with a hepatic biopsy revealing intrahepatic Budd–Chiari Syndrome. On (b) (6), abdominal angio-CT showed mesenteric ischemia and urgent operative intervention was indicated. Patient was transferred to a more specialized department and pegcetacoplan was discontinued. On (b) (6), patient received a single dose of eculizumab and was withdrawn from the study and underwent surgery. Patient clinically recovered from mesenteric ischemia. The investigator assessed the event of intestinal ischemia as possibly related to pegcetacoplan. The Applicant provides additional contributing etiologies, including related to underlying medical condition of PNH, renal failure secondary to hemolysis, and thrombosis secondary to catheter placement.

- Subject (b) (6): A 70-year-old male who experienced sepsis undocumented from biliary origin that resulted in hospitalization and was life-threatening. No relevant medical history or concomitant medication was reported. Patient was randomized to the pegcetacoplan group. On (b) (6) the patient received the last dose of pegcetacoplan prior to the event. The patient experienced sepsis, probably of biliary origin, pancreatitis, jaundice, and renal failure. Treatment included IV ceftriaxone and metronidazole. Blood cultures performed before and after antibiotic initiation were negative. One urinary culture was positive for *E. coli*, thought to be a possible contaminant given lack of leukocyturia. A second urinary culture was negative.

  On (b) (6), the patient experienced life-threatening hypoxia following a coughing crisis that required intensive care unit admission and improved with up to

12 L/min of oxygen therapy. No pulmonary lesions were found to explain hypoxia and event was deemed probably related to sepsis. On (b) (6), antibiotics were discontinued as patient was afebrile and sepsis event was thought to be resolved. The patient remained hospitalized due to persistent hemolysis and only partial recovery of renal failure. Pegcetacoplan was increased to every 3 days due to concurrent event of breakthrough hemolysis. The patient recovered. The investigator assessed biliary sepsis as possibly related to pegcetacoplan.

- Subject (b) (6): A 51-year-old male who experienced severe sepsis that resulted in hospitalization. The patient began study therapy on (b) (6) and was randomly assigned to the eculizumab treatment group on Study Day 15. On Study Day 127, the patient received Bexsero booster vaccination for meningitis. On Day 128, patient reported feeling unwell with nausea, sweating and difficulty in mobility. Patient presented to the emergency department with fever and vomiting later that day and admitted to hospital with IV antibiotics. Platelets were reported as 37. No sign of meningitis or hemolysis on admission. On Day 130, patient developed a rash with pain around the meningitis vaccine site. Platelets were recorded as 41 and reticulocytes as 2.5 (units and reference ranges not specified). The patient was discharged home on Day 130 and event was considered resolved. No changes to pegcetacoplan and eculizumab treatment due to the event of sepsis.
- Subject (b) (6): A 66-year-old male who experienced sepsis on Study Day 268 that resulted in hospitalization, diffuse large B-cell lymphoma on Study Day 278, and deep vein thrombosis on Day 285. The event of diffuse large B-cell lymphoma resulted in discontinuation. Medical history included aplastic anemia, iron overload, and basal cell carcinoma. On Study Day 1, patient was randomized to the pegcetacoplan study group and received first dose on Day 4. On Day 268, patient presented with hemoglobinuria and cough for 7 weeks with a temperature >38°C, chills, and hypotension. Patient was admitted to hospital and treated with IV antibiotics for sepsis. Laboratory results included LDH 1228 IU/L and hemoglobin 86 g/dL (reference range 135 to 180 g/dL). Chest X-ray revealed lateral focal opacity in the left upper zone. Blood cultures were performed. Patient was diagnosed with sepsis and moderate hemolysis. The investigator chose to remove the patient from the trial and taper pegcetacoplan.

  On Day 271, with ongoing cough and persistent fever, COVID-19 repeat polymerase chain reaction was negative and blood cultures negative after 48 hr. Repeat chest x-ray showed persistent opacity. Patient received prophylactic enoxaparin prophylaxis and antibiotics. On Day 273, with continued fever, a high-resolution chest portal venous phase abdominal and pelvic CT revealed a left pleural mass with supraclavicular adenopathy and splenomegaly. On Day 274, axillary lymph biopsy was performed. On Day 275, patient received a dose of pegcetacoplan. On Day 276, patient's polymerase chain reaction was positive for Epstein–Barr virus. Blood cultures showed no growth to date. On Day 277, positron emission tomography-CT revealed stage III high-grade lymphoma with confirmatory diagnosis on tissue biopsy. On Day 284 a central catheter was placed and patient was diagnosed with a deep vein thrombosis on Day 285 and treated with low-molecular-weight heparin. Patient was withdrawn from pegcetacoplan treatment, with the last dose on Day 296 and discontinued from study on Day 389 due to the event of diffuse large B-cell lymphoma.

No deaths or treatment-related SAEs were observed in Study APL2-307 up to the data cutoff of May 21, 2020. The most common SAE reported was hemolysis in two patients. There were no SAEs of sepsis. Infection SAEs comprised pharyngitis, skin infection, and urinary tract infection, which occurred in 1 of 45 (2.2%) patients, respectively. One of forty-five (2.2%) patients had an SAE of cerebral infarction.

In Study APL2-308, no deaths or treatment-related SAEs were observed up to the data cutoff. Of May 31, 2020. SAEs were neutropenia in 1 of 27 (3.7%) patients and dermoid cyst in 1 of 27 (2.7%) patients. One patient had an SAE of cellulitis.

18.1.9. Dropouts and/or Discontinuations Due to Adverse Events, APL2-202, APL2-204, and CP0514

Across all supportive studies, two subjects withdrew due to an AE. There were no deaths leading to study discontinuation. One subject withdrew because of a physician decision. Table 93 lists the AEs leading to study discontinuation.

Table 92. Adverse Events Leading to Discontinuation, Safety Population, APL2-202, APL2-204, CP0514

Adverse Event[1]	APL2-202 N=4 n (%)	APL2-204 N=22 n (%)	CP0514 N=9 n (%)
Discontinued Study	0 (0)	6 (27.3)	9 (100)
Death	0 (0)	0 (0)	0 (0)
Adverse event	0 (0)	2 (9.1)	0 (0)
Withdrawal by subject	0 (0)	3 (13.6)	1 (11.1)
Physician decision	0 (0)	1 (4.5)	0 (0)
Rollover to protocol APL2-307	0 (0)	0 (0)	4 (44.4)
Other	0 (0)	0 (0)	4 (44.4)

Source: Clinical data scientist and FDA clinical reviewer.
[1] Coded as Medical Dictionary for Regulatory Activities preferred terms.
Abbreviations: N, number of subjects in group; n, number of subjects with adverse event

18.1.10. Disposition and Discontinuations for Ongoing Studies

Seventy-seven subjects entered the open-label phase of Study APL2-302 (39 in the eculizumab group and 38 in the pegcetacoplan group from the RCP). Seventy-seven patients received at least one dose of pegcetacoplan. Sixty-seven patients completed treatment—32 patients (82.1%) in the crossover to pegcetacoplan group (28 weeks of pegcetacoplan monotherapy) and 35 patients (92.1%) in the pegcetacoplan continuation group (48 weeks of pegcetacoplan monotherapy).

In the open-label phase of Study APL2-302, 10 (13%) of subjects withdrew from study treatment because of an AE. Nine (11.7%) patients discontinued treatment or the study due to an AE. Seven (17.9%) of them were from the crossover to pegcetacoplan group and two (5.3%) from the pegcetacoplan continuation group. One subject discontinued pegcetacoplan treatment during the RCP and the study during the open-label period. One patient (1.3%) in the pegcetacoplan continuation group withdrew from study treatment due to physician decision; however, it was confirmed that this patient discontinued because of an AE of cytopenia.

During the open-label period, 10 patients withdrew from the study due to AEs: 7 (17.9%) in the crossover to pegcetacoplan group and 3 (7.9%) in the pegcetacoplan continuation group. The

AEs leading to discontinuation were pancytopenia, hemolysis (three patients), sepsis, intestinal ischemia, COVID-19, hypersensitivity pneumonitis, and hemolytic anemia. The patients who discontinued during the open-label phase are described below:

- Subject (b) (6) discontinued the study due to breakthrough hemolysis.
- Subject (b) (6) discontinued pegcetacoplan treatment and the study due to hemolysis.
- Subject (b) (6) discontinued the study because of pancytopenia.
- Subject (b) (6) discontinued pegcetacoplan treatment due to breakthrough hemolysis.
- Subject (b) (6) discontinued pegcetacoplan because of sepsis. A narrative is included in Section 18.1.7.
- Subject (b) (6) discontinued pegcetacoplan treatment and the study due to a severe SAE of intestinal ischemia. A narrative is included in Section 18.1.7.
- Subject (b) (6) had a fatal SAE of COVID-19 that led to discontinuation of pegcetacoplan treatment and the study.
- Subject (b) (6) discontinued pegcetacoplan treatment and the study because of a severe SAE of hypersensitivity pneumonitis (Section 18.1.7).
- Subject (b) (6) discontinued pegcetacoplan treatment and the study because of a severe SAE of hemolytic anemia (Section 18.1.7).

Sixty-seven patients (87%) completed study treatment and sixty-four patients (83.1%) entered the long-term safety and efficacy extension study (APL2-307) (32 patients from each group). Two subjects in the pegcetacoplan continuation group continued treatment with pegcetacoplan by means of a single-patient compassionate-use program and one patient in the pegcetacoplan continuation group chose not to enter the extension study.

No discontinuations were reported in Study APL2-307. There were no discontinuations due to AEs in Study APL2-308 as of data cutoff.

18.1.11. Treatment-Emergent Adverse Events, APL2-202, APL2-204, and CP0514

In total, three of four (75%) patients experienced a TEAE during Study APL2-202. The most common TEAEs were injection site reactions, erythema, and dizziness, which were seen in two of four (50%) patients.

In Cohort 2 of Study APL2-204, 18 of 20 (90%) patients receiving pegcetacoplan experienced a TEAE. The most common type of TEAE was infections, all seen in 9 of 20 (45%) patients. Injection site reactions, hemorrhage, and upper respiratory tract infection were frequent TEAEs reported in more than one patient in the pegcetacoplan group of the RCP.

In Study CP0514 (Cohort 4), six of six (100%) patients experienced a TEAE. The most frequently reported TEAEs in patients receiving eculizumab during the RCP were injection site reactions, headache, and hemorrhage, each reported in five of six (83%) patients. Pyrexia; infection, all; and liver enzyme abnormalities were frequently reported TEAEs in patients receiving eculizumab monotherapy. The frequency of TEAEs is shown in Table 94.

Table 93. Treatment-Emergent Adverse Events[1] Reported in ≥5% of Patients Treated with Pegcetacoplan, APL2-202, APL2-204, and CP0514

Adverse Event[2]	APL2-202 N=4 n (%)	APL2-204 Cohort 2 N=20 n (%)	CP0514 Cohort 4 N=6 n (%)
General disorders and administration site conditions			
Injection site reaction[3]	2 (50)	6 (30)	5 (83.3)
Allergic reaction[3]	0 (0)	0 (0)	1 (16.7)
Decreased appetite	0 (0)	0 (0)	1 (16.7)
Fever, rigors[3]	0 (0)	3 (15)	3 (50)
Accident[3]	0 (0)	1 (5)	1 (16.7)
Lethargy	0 (0)	1 (5)	1 (16.7)
Fatigue[3]	0 (0)	1 (5)	3 (50)
Infections, all[3]	1 (25)	9 (45)	4 (66.7)
Upper respiratory tract infection[3]	1 (25)	7 (35)	3 (50)
Herpes virus[3]	0 (0)	1 (5)	0 (0)
Viral infection[3]	0 (0)	1 (5)	2 (33.3)
Nasopharyngitis[3]	1 (25)	3 (15)	0 (0)
Influenza	0 (0)	0 (0)	2 (33.3)
Abscess[3]	0 (0)	1 (5)	0 (0)
Sepsis	0 (0)	0 (0)	1 (16.7)
Urinary tract infection	0 (0)	0 (0)	1 (16.7)
Gastrointestinal disorders			
Diarrhea	0 (0)	1 (5)	1 (16.7)
Abdominal pain[3]	0 (0)	2 (10)	3 (50)
Acute cholecystitis	0 (0)	1 (5)	0 (0)
Hepatic steatosis	0 (0)	1 (5)	0 (0)
Constipation	0 (0)	1 (5)	0 (0)
Hepatic injury[3]	0 (0)	1 (5)	3 (50)
Hyperbilirubinemia, alkaline phosphatase[3]	0 (0)	1 (5)	1 (16.7)
Vomiting	0 (0)	1 (5)	0 (0)
GI bleed[3]	0 (0)	0 (0)	1 (16.7)
Nausea	0 (0)	0 (0)	1 (16.7)
Pancreatitis	0 (0)	0 (0)	1 (16.7)
Blood and lymphatic system disorders			
Hemolysis[3]	1 (1.2)	4 (9.8)	11 (28.2)
Musculoskeletal disorders			
Muscle spasms	0 (0)	0 (0)	2 (33.3)
Fracture[3]	1 (25)	0 (0)	0 (0)
Arthralgia	0 (0)	1 (5)	0 (0)
Myalgia	0 (0)	0 (0)	2 (33.3)
Back pain	0 (0)	0 (0)	3 (50)
Vascular disorders			
Hemorrhage[3]	0 (0)	6 (30)	5 (83.3)
Ecchymosis, hematoma[3]	0 (0)	1 (5)	1 (16.7
Epistaxis	0 (0)	3 (15)	0 (0)
Abnormal uterine bleeding[3]	0 (0)	1 (5)	0 (0)
Portal vein thrombosis	0 (0)	0 (0)	1 (16.7)
Hematuria	0 (0)	2 (10)	0 (0)

Adverse Event[2]	APL2-202 N=4 n (%)	APL2-204 Cohort 2 N=20 n (%)	CP0514 Cohort 4 N=6 n (%)
Cardiovascular disorders			
Arrythmia[3]	0 (0)	1 (5)	0 (0)
Hypotension	0 (0)	1 (5)	0 (0)
Peripheral edema	0 (0)	1 (5)	1 (16.7)
QT prolonged	0 (0)	3 (15)	0 (0)
Renal and urinary disorders			
Acute kidney injury	0 (0)	2 (10)	0 (0)
Polyuria	0 (0)	0 (0)	1 (16.7)
Stone, renal colic[3]	0 (0)	0 (0)	1 (16.7)
Ophthalmology disorders			
Eye other[3]	0 (0)	0 (0)	1 (16.7)
Cataract	0 (0)	1 (5)	0 (0)
Diplopia	0 (0)	0 (0)	1 (16.7)
Visual disturbance[3]	0 (0)	0 (0)	2 (33.3)
Malignancy			
Abdominal neoplasm	0 (0)	1 (5)	0 (0)
White blood cell disorders			
Thrombocytopenia	0 (0)	2 (10)	0 (0)
Leukopenia[3]	0 (0)	4 (20)	1 (16.7)
Blood and lymphatic disorders			
Iron deficiency[3]	0 (0)	1 (5)	0 (0)
Aplastic anemia	0 (0)	1 (5)	0 (0)
Anemia[3]	0 (0)	1 (5)	1 (16.7)
Hemolysis[3]	0 (0)	5 (25)	0 (0)
Respiratory disorders			
Pneumonitis	0 (0)	1 (5)	0 (0)
Cough[3]	1 (25)	2 (10)	1 (16.7)
Metabolism and nutrition disorders			
Diabetes, glucose intolerance, hyperglycemia[3]	0 (0)	0 (0)	1 (16.7)
Hypomagnesemia	0 (0)	0 (0)	1 (16.7)
Hypocalcemia	0 (0)	1 (5)	1 (16.7)
Hypokalemia	0 (0)	4 (20)	1 (16.7)
Neurologic disorders			
Paresthesia[3]	0 (0)	1 (5)	1 (16.7)
Somnolence[3]	0 (0)	1 (5)	1 (16.7)
Dizziness	2 (50)	2 (10)	1 (16.7)
Headache	0 (0)	0 (0)	5 (83.3)
Investigational laboratory tests			
Got, gpt, ggtp, lfts[3]	0 (0)	3 (15)	4 (66.7)

Adverse Event[2]	APL2-202 N=4 n (%)	APL2-204 Cohort 2 N=20 n (%)	CP0514 Cohort 4 N=6 n (%)
Dermatology disorders			
Erythema[3]	2 (50)	4 (20)	3 (50)
Rash[3]	0 (0)	3 (15)	3 (50)
Alopecia	0 (0)	0(0)	1 (16.7)
Urticaria	0 (0)	0 (0)	1 (16.7)
Pruritus[3]	1 (25)	0 (0)	2 (33.3)

Source: Clinical data scientist and FDA clinical reviewer.
[1] Treatment-emergent adverse events defined as 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. If more than one AE with the same PT was reported before the date of the first dose, then the AE with the greatest severity was presented in summaries. An AE that occurred more than 30 days after the date of the last dose was not counted as a TEAE.
[2] Coded as Medical Dictionary for Regulatory Activities preferred terms.
[3] The following terms were combined:
Abdominal pain includes: abdominal pain upper, abdominal discomfort, abdominal pain
Abnormal uterine bleeding includes: uterine hemorrhage
Abscess includes nasal abscess
Accident includes: road traffic accident, fall
Anemia includes: hemolytic anemia, anemia
Arrythmia includes: bradycardia
Coagulopathy includes: activated partial thromboplastin time prolonged
Cough includes: cough, productive cough
Diabetes, glucose intolerance, hyperglycemia includes: blood glucose increased
Erythema includes: injection site erythema, erythema, generalized erythema
Fatigue includes: malaise, asthenia, lethargy, fatigue
Fever, rigors includes: febrile neutropenia, pyrexia, body temperature increased
Fracture includes: rib fracture
GI bleed includes: lower gastrointestinal hemorrhage, rectal hemorrhage
Got, gpt, ggtp, lfts includes: alanine aminotransferase increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, transaminases increased
Hemolysis includes: hemolysis, hemolytic anemia, hemoglobinuria, intravascular hemolysis
Hemorrhage includes: PT injection site bruising, contusion, epistaxis, hematoma, conjunctival hemorrhage, gingival bleeding, petechiae, post procedural hemorrhage, purpura, ecchymosis, infusion site bruising, injection site hemorrhage, lower gastrointestinal hemorrhage, rectal hemorrhage, hematuria
Hepatic injury includes: alanine aminotransferase increased, aspartate aminotransferase increased
Herpes virus includes: ophthalmic herpes zoster
Hyperbilirubinemia, alkaline phosphatase includes: PT=blood a kaline phosphatase increased, hyperbilirubinemia
Infection, all includes: influenza-like illness, nasopharyngitis, rhinitis, cholangitis, acute cholecystitis, hordeolum, nasal abscess, ophthalmic herpes zoster, paronychia, pharyngitis, influenza, sepsis, upper respiratory tract infection, ear infection, urinary tract infection
Injection site reaction includes: injection site erythema, injection site swelling, injection site induration, injection site bruising, injection site pain, injection site pruritus, administration site swelling, injection site hemorrhage, injection site edema, injection site warmth
Iron deficiency includes: serum ferritin decreased
Leukopenia includes: febrile neutropenia, neutropenia, neutrophil count decreased, white blood cell count decreased
Nasopharyngitis includes: nasopharyngitis, rhinitis, pharyngitis
Paresthesia includes: hypoesthesia, burning sensation
Pruritus includes injection site pruritus, eye pruritus, pruritus
Rash includes: rash, rash maculopapular, urticaria
Somnolence includes: lethargy
Stone, renal colic includes: nephrolithiasis
Upper respiratory tract infection includes: influenza like illness, nasopharyngitis, rhinitis, pharyngitis, upper respiratory tract infection
Viral infection includes: ophthalmic herpes zoster, influenza
Visual disturbance includes: vision blurred
Abbreviations: N, number of subjects; n, number of subjects with adverse event; PT, preferred term; QT, QT interval

18.1.12. Treatment-Emergent Adverse Events for Ongoing Study APL2-302 Open-Label Phase

Per the Applicant, the majority of patients (70 [90.9%]) had at least one TEAE. The incidence of TEAEs was similar between the crossover to pegcetacoplan group (37 patients [94.9%)] and the pegcetacoplan continuation group (33 patients [86.8%]). Most TEAEs (68.9%) were mild or moderate; 22.1% were severe. The most common severe TEAEs (at least two subjects in the total pegcetacoplan group) were hemolysis (eight patients [10.4%]), acute kidney injury (three subjects [3.9%]), hemolytic anemia (two patients [2.6%]), and acute respiratory failure (two patients [2.6%]). The most common TEAEs reported as drug-related were injection site erythema (nine patients [11.7%]), injection site induration (five patients [6.5%]), injection site pruritus (four patients [5.2%]), headache (four patients [5.2%]), pyrexia (three patients [3.9%]), and hyperbilirubinemia (three patients [3.9%]).

The TEAEs that occurred in ≥5% of patients were similar between the crossover to pegcetacoplan group and the pegcetacoplan continuation group. Injection site erythema and fatigue were more frequent in the crossover to pegcetacoplan continuation group. With the exception of hemolysis, most common TEAEs were mild to moderate. The most common TEAEs experienced in ≥5% of patients were hemolysis (19.5%), nasopharyngitis 15.6%), diarrhea (13%), injection site erythema (11.7%), fatigue (11.7%), upper respiratory tract infection (10.4%), headache (10.4%), and cough (10.4%).

18.1.13. Laboratory Findings, APL2-202, APL2-204, and CP0514

Hematology

Overall, in the supportive trials, the hematology laboratory findings were consistent with those expected in PNH. In Study APL2-202, per the Applicant, clinically significant out-of-range laboratory values consist with a diagnosis of PNH (low erythrocyte counts, low hematocrit levels, and high free hemoglobin levels) as determined by the investigator were seen intermittently in three patients.

In Study APL2-204, 2 of 20 (10%) of patients experienced a TEAE of thrombocytopenia. Four of twenty (20%) patients experienced a TEAE of leukopenia. In Cohort 4 of Study CP0514, one of six (16.7%) patients experienced a TEAE of anemia and leukopenia.

Chemistry

During Study APL2-202, ALT and AST levels decreased. ALT level decreased from a mean of 23.3 U/L at baseline to 16 U/L at Day 365, for a mean CFB of -7.3 U/L. AST level also decreased from a mean of 108.3 U/L at baseline to 24 U/L at Day 8. By Day 365, AST level was 17 U/L, which represented a mean CFB of -91.3 U/L. Direct bilirubin and total bilirubin levels decreased by Day 365 by means of -2.6 and -21.5 μmol/L, respectively. After pegcetacoplan dosing, two subjects reported intermittent clinically significant out-of-range chemistry laboratory values for ferritin, which we considered to be consistent with a diagnosis of PNH and transfusion dependence, per the Applicant.

In Cohort 2 of Study APL2-204, 3 of 20 (15%) patients experienced a TEAE of abnormal liver enzymes. In Cohort 4 of Study CP0514, a trend of increased ALT with repeated dosing of pegcetacoplan was not noted. Four of six (66.7%) patients experienced abnormal liver enzymes.

Urinalysis

During Study APL2-202, four subjects had sporadic out-of-range results for urinalysis parameters that each resolved without any interruptions in dosing.

In Cohort 2 of Study APL2-204, there was no abnormal urinalysis laboratory data reported. In Study CP0514, one subject with a history of periodic urinary tract infections experienced a TEAE of urinary tract infection. Overall, there were minimal urinalysis findings that represented a CFB of normal to abnormal per the Applicant.

Coagulation

During Study APL2-202, four patients had out-of-range coagulation parameters, but none was considered clinically significant and none was reported as a TEAE per the Applicant.

In Cohort 2 of Study APL2-204, there was no individually clinically significant coagulation abnormality. In Study CP0514, there were isolated instances of abnormal coagulation parameter findings in Cohort 4 patients. Two events of prolonged activated partial thromboplastin time were reported prior to changing laboratory equipment, which had consistently prolonged activated partial thromboplastin time due to interference of a reagent with pegcetacoplan. Therefore, these results were not considered to be clinically relevant.

Vital Signs

In Study APL2-202, no subject had an abnormal temperature reading and none of the vital sign parameters were assessed as clinically significant and none were reported as TEAEs.

In Cohort 2 of APL2-204, 3 of 20 (15%) patients had one or more diastolic blood pressure measurements ≥95 mm Hg and 2 of 20 (10%) had one or more systolic blood pressure measurements ≥165 mm Hg. In Study CP0514, there were isolated abnormal vital sign readings for systolic blood pressure, diastolic blood pressure, pulse rate, and respiratory rate, but none of these abnormal readings were determined to be clinically significant per the Applicant. Three of six (50%) patients experienced a TEAE of fever or rigors.

ECG

In Study APL2-202, four patients had ECG findings interpreted as abnormal during the study. None of these was reported as a TEAE.

In Cohort 2 of Study APL2-204, 3 of 20 (15%) patients experienced a TEAE of QTc prolongation. In Cohort 4 of Study CP0514, there was one ECG finding considered to be clinically significant. Subject (b) (6) had an abnormal ECG finding at baseline with a QTc of 463 ms. On Day 1 of dosing, at 2 hr postdose, an anterior infarct was noted. There was no predose ECG performed. The subject was referred to a cardiologist, who reviewed the data and concluded that dosing with pegcetacoplan could continue per protocol.

Immunogenicity

In Study APL2-202, the incidence of antipegcetacoplan peptide and anti-polyethylene glycol antibodies was 0% and 25% (one of four patients), respectively. The development of a treatment-emergent anti-PEG antibody response was considered transient in this study.

In Cohort 2 of Study APL2-204, two subjects had a confirmed positive result for antipegcetacoplan peptide antibodies at baseline, with a titer of 1:10. Two patients developed a treatment-emergent anti-PEG antibody response, which were considered transient by the Applicant. Three subjects developed a treatment-boosted anti-PEG antibody response with an at least four-fold increase in titer compared to that predose. Per the Applicant, there was no observed association of antibody development with a clinical response or AEs, except one patient who developed a mild maculopapular rash on Day 33 that was temporally related to a transient, treatment-emergent anti-PEG antibody response observed on Day 29. Both the event and the antibody response resolved without interruption to pegcetacoplan treatment.

In Study CP0514, one subject in Cohort 3 tested positive for antidrug antibody on Days 57, 71, and 85. This subject then participated in Cohort 4 and tested positive (inhibition 69.2%) at baseline. All other results were negative.

19. Mechanism of Action/Drug Resistance: Additional Information and Assessment

Not applicable.

20. Other Drug Development Considerations: Additional Information and Assessment

Not applicable.

21. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

The Division requested that Office of Scientific Investigations inspect a single clinical study clinical investigator site, a U.S. site with the largest number of reported protocol deviations. The Division also requested inspection of the Applicant's site to assess clinical trial oversight adequacy. Dr. Anthony Orencia, Dr. Min Lu, and Dr. Kassa Ayalew from the Office of Scientific Investigations provided the clinical inspection summary.

Clinical data from a single study, APL-302, were submitted to the Agency in support of NDA 215014 for pegcetacoplan. A single clinical investigator site (Ilene Weitx, M.D.) and the Applicant's site (Apellis Pharmaceuticals, Inc.) were inspected in support of this application.

OSI did not identify significant deficiencies among the available records. Based on these inspections, the study data derived from Dr. Ilene Weitz, the clinical investigator site, and the

Applicant's site are considered reliable. The data from Study APL2-302 submitted to the FDA appear acceptable in support of this NDA and the proposed indication.

22. Labeling Summary of Considerations and Key Additional Information

Table 94. Proposed Labeling Revisions

Section	Revision Proposed
Throughout Labeling	Added comma to all >4-digit numbers per ISMP. Revised text to avoid passive voice. Revised text to avoid referring to patients by their disease.
Highlights of PI	Revised product title per guidance. Revised boxed warning to be consistent with class boxed labeling. Added dosage form "Injection" as header of Dosage Forms and Strengths. Updated title of warning to "Infusion-Related Reactions" to be consistent with other product labeling. Revised list of most common adverse reactions to remove extraneous language and be consistent with Guidance. Updated all sections to be consistent with FPI.
1 Indications and Usage	No change.
2 Dosage and Administration	Relocated text inserted between main heading and numbered subheading as this text will not be listed in TOC. Text moved to 2.4. Revised 2.1 (recommended vaccination) to be consistent with other complement inhibitor labeling. Reorganized location of text to keep similar topics together. Requested Applicant to provide specific instructions for patients switching from other complement inhibitors with regards to timing. Requested that Applicant include instructions for dose-adjustments, missed doses, and dose delays, as they were conducted in trial.
3 Dosage Forms and Strengths	Revised to provide the dosage form as a heading.
4 Contraindications	Recommended the addition of a CI for unvaccinated patients.
5 Warnings and Precautions	Removed text (b) (4) We made the REMS into a separate W&P per Guidance. We asked the Applicant to revise the warnings to provide examples of types of reactions that occurred, a numerical estimate of the incidence/rate, known risk factors for the reaction, and steps to prevent, mitigate, monitor for, or manage the reaction; per the Guidance.
6 Adverse Reactions	Removed (b) (4) to be consistent with other complement inhibitor labeling. Added text that lists most common serious ARs. Revised the main AR table to be consistent with our current approach and use FDA MedDRA queries to assess safety. We removed (b) (4) We removed (b) (4) per AR guidance. (b) (4) We removed (b) (4) Immunogenicity subsection was updated to reflect our current approach.
7 Drugs Interactions	No subsection included; no relevant interactions to report.

Section	Revision Proposed
8 Use in Specific Populations	Revised text to be consistent with Guidances.
10 Overdosage	No subsection; no relevant information to include.
11 Description	Requested that Applicant insert structure, molecular formula, and molecular weight.
12 Clinical Pharmacology	MoA: Removed (b) (4) PD: Removed (b) (4) Revised Cardiac EP text to reflect standard approach. PK: Requested that Applicant add an introductory paragraph describing general PK properties and any unique characteristics. Recommended including hepatic function tests (range of values) tested in PopPK analysis.
13 Nonclinical Toxicology	Revised for brevity and clarity.
14 Clinical Studies	Revised per Guidance and for clarity. Removed (b) (4) (b) (4) descriptions per Guidance. Recommended removal (b) (4) Removed some text (b) (4) (b) (4)
15 References	NA
16 How Supplied/Storage and Handling	Revised text to improve description of the product packaging and include a placeholder for NDC.
17 Patient Counseling	We revised the order of symptoms of infection based on likelihood of symptoms.

Source: Clinical Reviewer
Abbreviations: AR, adverse reaction; EP, electrophysiologist; FPI, full prescribing information; HCP, health care practitioner; ISMP, Institute for Safe Medication Practices; MedDRA, Medical Dictionary for Regulatory Activities; MoA, mechanism of action; NA, not applicable; NDC, new drug code; PI, prescribing information; PD, pharmacodynamic; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria; PopPK, population pharmacokinetic; REMS, Risk Evaluation and Mitigation Strategy; TOC, table of contents; W&P, Warnings and Precautions

23. Postmarketing Requirements and Commitments

The clinical postmarketing requirements (PMRs) outlined below are recommended.

PMR 1

Establish a registry to characterize the long-term safety of pegcetacoplan in adult patients with PNH, including patients who are treatment naïve, with at least 5 years of follow-up. Submit yearly safety follow-up data and a summary of the major safety findings for all patients, including the development or worsening of autoimmune diseases such as systemic lupus erythematosus and/or all serious infections with encapsulated bacteria. The final study report should include an integrated safety dataset and patient level data including data on pegcetacoplan dosing, meningococcal and pneumococcal vaccination status and concomitant medications.

Scheduled milestones:

- Interim Report #1: March 2023
- Interim Report #2: March 2024
- Interim Report #3: March 2025
- Interim Report #4: March 2026
- Interim Report #5: March 2027
- Interim Report #6: March 2028
- Study/Trial Completion: January 2029
- Final Report Submission: July 2029

PMR 2

Complete Study APL2-302, *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)*. Include updated summary of safety and efficacy analysis and submit datasets at the time of final clinical study report submission.

Scheduled milestones:

- Final Report Submission: September 2021

PMR 3

Complete Study APL2-307, *An Open-Label, Nonrandomized, Multicenter Extension Study to Evaluate the Long-Term Safety and Efficacy of Pegcetacoplan for the Treatment of PNH in Patients Who Have Completed Another Pegcetacoplan Clinical Study*. Include an updated summary of safety and efficacy analysis and submit datasets at the time of final clinical study report submission.

Scheduled milestones:

- Interim Report: June 2022
- Study/Trial Completion: August 2025
- Final Report Submission: February 2026

PMR 4

Complete Study APL2-308, *A Phase 3, Randomized, Multicenter, Open-Label, Controlled Study to Evaluate the Efficacy and Safety of Pegcetacoplan as Monotherapy Compared to Standard of Care (Excluding Complement Inhibitors) in Patients with PNH*. Include an updated summary of the safety and efficacy analyses and submit datasets at the time of final clinical study report submission.

Scheduled milestones:

- Study/Trial Completion: October 2021
- Final Report Submission: April 2022

The OBP postmarketing commitments (PMCs) outlined below are recommended.

PMC 1

Develop a sensitive assay to detect and monitor the presence and titer of antibodies that bind the active moiety of pegcetacoplan. The assay should be capable of detect neutralizing antipegcetacoplan antibodies (ADA) in the presence of pegcetacoplan levels that are expected to be present in serum at the time of patient sampling. The final report should include development and validation data to support use of the assay.

Scheduled milestones:

- Draft Protocol Submission: July 2021
- Final Protocol Submission: November 2021
- Final Report Submission: May 2023

PMC 2

Develop and validate a sensitive assay to evaluate the neutralizing activity of antipegcetacoplan antibodies (ADA) detected in patient samples. The assay should be capable of sensitive detection of neutralizing ADA in the presence of pegcetacoplan levels that are expected to be present in serum at the time of patient sampling. The final report should include development and validation data to support use of the assay.

Scheduled milestones:

- Draft Protocol Submission: July 2021
- Final Protocol Submission: November 2021
- Final Report Submission: May 2023

PMC 3

Use the sensitive assays developed under PMCs 1 and 2 to establish the incidence, titer, and neutralizing activity of antibodies to pegcetacoplan in patient samples from Studies APL2-302, APL2-307, and APL2-308. Establish whether there is an impact of antibodies on safety and efficacy of pegcetacoplan. Submit datasets at the time of final report submission.

Scheduled milestones:

- Draft Protocol Submission: July 2023
- Final Protocol Submission: November 2023
- Final Report Submission: August 2026

24. Financial Disclosure

The Applicant provided certification on FDA Form 3454 to indicate that there were no financial arrangements between the Applicant and Investigators that could be affected by the outcome of the Phase 3 Studies APL2-302, APL2-202, APL2-204, and CP0514. For the one investigator whose financial disclosure form could not be obtained, the Applicant provided a certification attesting to the Applicant's due diligence in attempting to obtain the information, and the reason why such information was not obtained.

Table 95. Covered Clinical Studies: APL2-302, APL2-202, APL2-204, CP0514

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 366 Enter text here.		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 1 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3):		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

25. References

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26. Review Team

Table 96. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Carleveva Thompson
Nonclinical Reviewer	Fred Alavi
Nonclinical Team Leader	Todd Bourcier
Office of Clinical Pharmacology Reviewer(s)	Li Li, Brianna Cote, Jihye Ahn, Justin Earp
Office of Clinical Pharmacology Team Leader(s)	Sudharshan Hariharan
Clinical Reviewer	Julie Weisman
Clinical Team Leader	Tanya Wroblewski
Statistical Reviewer	Sara Jimenez
Statistical Team Leader	Yeh-Fong Chen
Cross-Disciplinary Team Leader	Tanya Wroblewski
Division Director (pharm/tox)	Todd Bourcier
Division Director (OCP)	Doanh Tran
Division Director (OB)	Thomas Gwise
Associate Division Director (clinical)	Albert Deisseroth
Office Director (or designated signatory authority)	Ellis Unger

OCP, Office of Clinical Pharmacology
OB, Office of Biostatistics

Table 97. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Theodore Carver, Marco Cardone, Daniela Verthelyi
Microbiology	Maritere Carattini, Erika Pfeiler
OPDP	Rebecca Falter
OSI	Anthony Orencia, Min Lu, Kassa Ayalew
OSE/DEPI	Steven Bird
OSE/DMEPA	Stephanie DeGraw, Hina Mehta
OSE/DRISK	Naomi Boston, Brad Moriyama
CDRH	Matthew Ondeck, Jake Lindstrom, Marc Neubauer
Other	Susan Redwood

OPQ, Office of Pharmaceutical Quality
OPDP, Office of Prescription Drug Promotion
OSI, Office of Scientific Investigations
OSE, Office of Surveillance and Epidemiology
DEPI, Division of Epidemiology
DMEPA, Division of Medication Error Prevention and Analysis
DRISK, Division of Risk Management

Table 103. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Julie Weisman, MD	OND/DNH	Sections 2.3, 2.4, 2.6.3, 2.7, 3.15, 3.17, 3.22, 3.23, 3.24 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Julie K. Weisman -S Digitally signed by Julie K Weisman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002348674, cn=Julie K Weisman -S Date: 2021.05.11 10:39:45 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Tanya Wroblewski, MD	OND/DNH	Sections 2.3, 2.4, 2.6.3, 2.7, 3.15, 3.17, 3.22, 3.23, 3.24 ☐ Authored ☐ Contributed ☒ Approved
Cross-Disciplinary Team Lead	**Signature:** Tanya M. Wroblewski -S3 Digitally signed by Tanya M. Wroblewski -S3 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011605845, cn=Tanya M. Wroblewski -S3 Date: 2021.05.14 09:14:55 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Albert Deisseroth, MD, PhD	OND/DNH	All Sections ☐ Authored ☐ Contributed ☒ Approved
Supervisory Associate Director	**Signature:** Albert B. Deisseroth -S Digitally signed by Albert B. Deisseroth -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000589069, cn=Albert B. Deisseroth -S Date: 2021.05.14 12:07:31 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Fred Alavi, PhD	OND/DPTOCHEN	Sections 5.1; 7.1; 8.4; 13 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Fred K. Alavi -S Digitally signed by Fred K. Alavi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Fred K. Alavi -S, 0.9.2342.19200300.100.1.1=1300145143 Date: 2021.05.11 10:59:19 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Continued: Table 103. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Todd Bourcier, PhD	OND/DPTOCHEN	Sections: 5.1; 7.1; 8.4; 13 ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** Todd M. Bourcier -S Digitally signed by Todd M. Bourcier -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235462, cn=Todd M. Bourcier -S Date: 2021.05.11 12:49:44 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Li Li, PhD	OND/OCP/DCEP	Sections 5, 6.1, 6.3, 8.1, 8.2, 14.2, 14.4, 18.1.13 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Li Li -S Digitally signed by Li Li S DN: c US o U S Government ou HHS ou FDA ou People cn Li Li S 0 9 2342 19200300 100 1 1 2000508577 Date: 2021 05 11 14:16:05 04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Brianna Cote, PharmD, PhD	OND/OCP/DCEP	Section 14.1 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Brianna M. Cote -S Digitally signed by Brianna M. Cote -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2003141450, cn=Brianna M. Cote -S Date: 2021.05.12 11:50:00 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Jihye Ahn, PharmD	OND/OCP/DPM	6.1, 6.3, 14.3 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Jihye Ahn -S (Affiliate) Digitally signed by Jihye Ahn S (Affiliate) DN: c=US, o=U S Government, ou=HHS, ou=FDA, ou=People, 0 9 2342 19200300 100 1 1=2001814798, cn=Jihye Ahn S (Affiliate) Date: 2021 05 12 11:19:03 04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Continued: Table 103. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Justin Earp, PhD	OND/OCP/DPM	6.1, 6.3, 14.3 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Justin C. Earp -S Digitally signed by Justin C. Earp -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Justin C. Earp -S, 0.9.2342.19200300.100.1.1=1300436664 Date: 2021.05.13 22:14:56 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Sudharshan Hariharan, PhD	OND/OCP/DCEP	Sections 5, 6.1, 6.3, 8.1, 8.2, 14, 18.1.13 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature: Signed on behalf of Sudharshan Hariharan** Doanh C. Tran -S Digitally signed by Doanh C. Tran -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Doanh C. Tran -S, 0.9.2342.19200300.100.1.1=1300378169 Date: 2021.05.13 17:39:33 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Doanh Tran, PhD	OND/OCP/DCEP	Sections 5, 6.1, 6.3, 8.1, 8.2, 14, 18.1.13 ☐ Authored ☐ Contributed ☒ Approved
Deputy Director	**Signature:** Doanh C. Tran -S Digitally signed by Doanh C. Tran -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Doanh C. Tran -S, 0.9.2342.19200300.100.1.1=1300378169 Date: 2021.05.13 17:41:29 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Sara Jimenez, PhD	OB/DBIX	Sections 6.2, 16 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Sara Jimenez -S Digitally signed by Sara Jimenez S DN: c=US o=U S Government ou=HHS ou=FDA ou=People cn=Sara Jimenez S 0 9 2342 19200300 100 1 1=2002241423 Date: 2021 05 11 16:11:22 04 00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Continued: Table 103. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Yeh-Fong Chen, PhD	OB/DBIX	Sections 6.2, 16 ☐ Authored ☒ Contributed ☐ Approved
Team Leader	**Signature:** Yeh Fong Chen -S Digitally signed by Yeh Fong Chen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yeh Fong Chen -S, 0.9.2342.19200300.100.1.1=1300157970 Date: 2021.05.11 16:29:57 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Thomas Gwise, PhD	OB/DBIX	Sections 6.2, 16 ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** Thomas E. Gwise -S Digitally signed by Thomas E. Gwise -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300369224, cn=Thomas E. Gwise -S Date: 2021.05.11 17:04:17 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Continued: Table 103. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Carleveva Thompson, MS	ORO/DROCHEN	Section 12 ☒ Authored ☐ Contributed ☐ Approved
Regulatory Project Manager	**Signature:** Carleveva Thompson Digitally signed by Carleveva Thompson DN: cn=Carleveva Thompson, o=US Food and Drug Administration, ou=CDER, email=Carleveva.Thompson@fda.hhs.gov, c=US Date: 2021.05.14 10:06:11 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Charlene Wheeler, MSHS	ORO/DROCHEN	Section 12 ☐ Authored ☒ Contributed ☒ Approved
Chief, Project Management Staff	**Signature:** Charlene N. Wheeler -S Digitally signed by Charlene N. Wheeler -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000621384, cn=Charlene N. Wheeler -S Date: 2021.05.14 10:09:50 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARLEVEVA J THOMPSON
05/14/2021 02:28:18 PM

ELLIS F UNGER
05/14/2021 02:47:18 PM
This joint assessment represents the work of the review team for NDA 215014.