CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215014Orig1s000

OTHER REVIEW(S)

Memorandum of Review

STN	505(b)(1) NDA215014
Submit Date	04/01/2021
Received Date	04/15/2021
PDUFA Goal Date	05/14/2021
Subject	NDA 215014 Consult Request for ADA Assays
Division	DNH
Review Completion Date	05/07/2021
Product	Pegcetacoplan
Product Code Name	APL-2
Classification	Complement inhibitor
Applicant	Apellis Pharmaceuticals, Inc
Indication	Treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)
Dose Regime	1,080 mg/20mL solution for subcutaneous infusion, twice a week
Primary Reviewer	Marco Cardone, PhD Staff Scientist, OPQ/OBP/DBRR III
Secondary Reviewer	Daniela Verthelyi, MD, PhD Chief, Laboratory of Immunology, OPQ/OBP/DBRR III

Documents Reviewed

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Summary

Pegcetacoplan (APL-2) is a symmetrical molecule comprised of two identical pentadecapeptides covalently bound to the ends of a linear 40-kDa polyethylene glycol molecule (PEG40). The peptide moieties bind to complement C3 and C3b and exert a broad inhibition of the complement cascade. The PEG40 moiety imparts improved solubility and longer residence time in the body after administration of the drug. This PEGylated peptide is being developed for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH), a rare and chronic, life-threatening blood disorder associated with anemia due to hemolysis. The product is provided as a sterile, aqueous, (b) (4) sorbitol solution of 1080 mg/20 mL, to be administered via subcutaneous infusion twice a week. Pegcetacoplan received orphan drug designation from the FDA on April 20, 2014.

To assess the immunogenicity risk for pegcetacoplan, the Sponsor 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. The Sponsor also developed a neutralizing anti-drug antibody (NAb) assay to assess the neutralizing activity of detected ADA. However, the screening, titering, and neutralizing assays demonstrated low drug tolerance hindering detection and characterization of ADA. Thus, an adequate assessment of the incidence of ADA and their impact on pharmacokinetics, pharmacodynamics, safety, or efficacy of pegcetacoplan was not possible. To address these issues, three PMCs were proposed.

Consult

This is an NDA with immunogenicity data. DNH is requesting OBP to review the ADA assay validation data of the application.

Clinical Immunogenicity Finding

In the Phase 3 study APL2-302, around 46% (n:37/80) of patients had samples that screened positive for anti-pegcetacoplan peptide antibodies up to week 16, but only 2 of these were confirmed positive. The samples that confirmed positive had titers of 1:10. Of note, as stated above, the low drug tolerance for these assays suggests that the incidence of ADA may be underestimated and the titers higher than stated. In the same study, 68 out of 80 (85%) patients were confirmed positive for pre-existing or treatment-emergent (6 patients, 4 of which with treatment-boosted) anti-PEG antibodies. The titer of the samples ranged from 1:10 to 1:20500. The two patients with anti-pegcetacoplan peptide antibodies at week 16 also tested positive for anti-PEG antibodies from week 4 to week 16. It should be noted that the number of samples confirmed positive for anti-PEG antibodies exceeds what is reported in the literature and what was reported for the healthy donors; this could correspond to prior exposure to the peg moiety in this group of patient.

Confirmed positive samples for anti-pegcetacoplan peptide antibodies were also found in samples from Phase 1 studies 204conducted in PNH patients, and in studies 101 and 205 conducted in healthy volunteers or subjects with renal impairment. Among patients in study 204, which enrolled 17 patients, 7 patients had samples that screened positive, and 2 (11.8%) were confirmed as positive, however both had pre-existing antibodies and had low titers (1:10). Eight subjects in study 101 (n=40) screened positive for ADA and 3 of these confirmed positive for ADA (7.5%). Two of the confirmed positive samples were treatment-emergent responses at day 84 with titers ≤ 1:10 and one was positive prior to first dose. Subjects in study 205 confirmed positive for ADA were 1 out of 16 (6.3%) and showed pre-existing antibodies with titers of 1:40.
In these studies, as well as in trials 202 (Phase 2 study in PNH patients) and 102 (Phase 1 study in healthy volunteers), the Sponsor also confirmed incidence of pre-existing or treatment-emergent anti-PEG antibodies with rates between 25% and 85% (PNH patients) and 81-85% (healthy volunteers) and titers ranging from 1:10 to 1:20500 (PNH patients) and from 1:10 to 1:10240 (healthy volunteers).

Both patients with anti-pegcetacoplan peptide antibodies in the APL2-302 study and 2 of the 3 healthy volunteers with ADA response in the Phase 1 study 101 tested positive for NAbs (Clinical Information Amendment, module 1.11.3).

These ADA responses had no noticeable impact on the PK, PD, efficacy, or safety of pegcetacoplan.
In the APL2-302 study there were no ADA-related adverse events in either patients who confirmed positive for anti-drug antibodies or those who screened positive but confirmed negative.

However, since 1) circulating drug was shown to interfere with the detection of anti-pegcetacoplan peptide antibodies and their neutralization activity, 2) there is concern regarding the cut point for the confirmatory assay for ADA against the functional moiety of pegcetacoplan, and 3) the limited immunogenicity data available (up to 16 weeks), it is not possible to adequately assess the incidence of ADA and subsequent impact on PK, PD, safety, or effectiveness of pegcetacoplan.

Summary Basis of Recommendation/Executive Summary

Immunogenicity Executive Summary and Recommendation

To assess the immunogenicity potential of your drug product using Phase 3 clinical study samples from PNH subjects that received pegcetacoplan at the proposed dose regime (1,080 mg, twice weekly, SC), you developed an Anti-Pegcetacoplan Peptide Antibody Assay (Validation Report no. BAL-17-143-048-REP) and an Anti-PEG Antibody Assay (Validation report no. BAL-17-143-050-REP). You also used these assays to test samples from the Phase 1 studies 101, 205, and 102. In addition, you developed a Neutralizing Anti-Drug Antibody Assay (Validation Report no. BAL-17-143-027-REP) to assess the neutralizing activity of ADA in applicable samples tested positive for anti-pegcetacoplan peptide antibodies. You submitted these ADA assay validation reports in module 5.3.1.4, together with an Integrated Immunogenicity Summary in module 2.7.1, a Summary of Immunogenicity Results in module 2.7.2, and NAb results in module 1.11.3 (Clinical Information Amendment). Below is the summary of deficiencies, comments, and review of the ADA assay validation reports mentioned.

Information request submitted to Applicant on April 30th

Regarding your Anti-Pegcetacoplan Peptide Antibody Assay (Validation report no. BAL-17-143-048-REP) and Neutralizing Anti-Drug Antibody Assay (Validation report no. BAL-17-143-027-REP) used to test immunogenicity samples from the Phase 3 clinical study APL2-302, the Agency requested On April 30th, 2021 the following clarifications:

Question 1: According to your submission, the mean (%CV) serum steady-state trough concentrations of pegcetacoplan range between 655 (18.6%) µg/mL at Week 2 to 706 (15.1%) µg/mL at Week 16 in patients with PNH. Your data assessing matrix interference showed that HPC, MPC, and LPC tolerate up to 500, 62.5, and 0.244 µg/mL of on-board drug, respectively. Therefore, the ability of your assay to detect anti-pegcetacoplan peptide antibodies in the presence of circulating drug raises a concern. Please clarify.

Question 2: Regarding your screening assay, please clarify
a. whether the HPC, MPC and LPC are the rabbit antibody against the functional peptide of pegcetacoplan. Is this antibody a monoclonal antibody?
b. whether pretreatment with streptavidin-coated magnetic beads plus biotinylated PEG, to separate supernatants for downstream analysis from anti-PEG antibodies, is performed only on the diluted serum samples or is also performed for the controls. If controls are pretreated with beads, clarify how the expected concentration of the HPC, MPC, and LPC (rabbit anti-APL-2 antibody) is verified after separation.

Question 3: Regarding your confirmatory assay, the runs used to assess precision (Table 21, Validation Report no. BAL-17-143-048-REP), 6 out of 27 (22%) LPC (35 ng/mL, mean %Inhibition) scored below the CCP. This indicates that CCP and/or LPC may not have been set correctly. Please clarify

At the TC of May 3rd, 2021, you acknowledged the Agency's concerns and indicated that the assessment for ADA against pegcetacoplan peptide in clinical samples was still feasible because the sampling schedule included time points when drug tolerance was not an issue. At these time points, when anti-pegcetacoplan peptide antibodies could be reliable detected, a low percentage of subjects were confirmed positive after repeated SC doses of the drug product. In addition, at the end of follow-up visits after dosing discontinuation, 8 subjects who received pegcetacoplan treatment up to 296 days were all confirmed negative. You also indicated that the immunogenicity profile of pegcetacoplan in Phase 3 study patients is consistent with that observed in healthy volunteers with sampling schedule at time points when on-board drug is not an issue. You concluded that anti-pegcetacoplan peptide antibodies occurred infrequently, with low titers, and with no discernable impact on PK, PD, efficacy, or safety. You also clarified that the PC used in the anti-pegcetacoplan peptide antibody assay is a rabbit polyclonal antibody directed against the functional moiety of the drug product and confirmed that PC controls are pre-treated as the diluted serum samples to separate supernatants for downstream analysis, but their concentration is not verified after separation (also indicating that recovery studies were not performed after extraction). To answer question 3, you confirmed that the CCP was set correctly and that with this LPC the assay is conservative and may be slightly prone to rejects runs with less sensitivity.

The Agency acknowledged your answers and requested the submission of a table that includes number (%) of subjects screened positive, confirmed positive, and screened but not confirmed positive for anti-pegcetacoplan peptide antibodies and anti-PEG antibodies. The Agency also requested to specify in the table ADA titer and times in which study subjects were confirmed positive for ADA, as well as the nature of ADA (pre-existing, treatment-boosted, or treatment-induced).
The Agency expressed concerns about the drug tolerance of the NAb assay. You acknowledged the concern and indicated that the complement C3 may contribute to the low drug tolerance. You also indicated that only samples confirmed positive for ADA and with low circulating drug concentration will be tested for the presence of neutralizing antibodies. The Agency requested to submit or help to locate the development study data for the NAb assay to ensure that the assay detect optimal neutralization ability of observed ADA. In addition, you were asked to provide data for the CP determination, sensitivity, and precision of the tests of pivotal study samples.

<u>Additional requests issues during the meeting of May 3rd, 2021:</u>
The Assessors' comments to your responses to the questions raised at the TC of May 3rd are as follows.
QUESTION 1: Provide a table to summarize the anti-pegcetacoplan antibody (ADA) screening and confirmation results. Please specify in the table the titer and time point for study subjects confirmed positive for ADA, as well as the nature of ADA (pre-existing, treatment-boosted, or treatment-induced).
Please also include a similar table for the anti-PEG antibody assessment.
In addition, please submit or help to locate the development study data for the NAb assay and the NAb activity curve and provide data on CP determination, sensitivity, and precision of the tests of pivotal study samples.

As requested, on May 6th, 2021 (module 1.11.3, Clinical Information Amendment), you provided two tables showing the incidence of anti-pegcetacoplan peptide antibodies (Table 1, below) and anti-PEG antibodies (Table 2, below) evaluated in 6 clinical study subjects, including the 80 PNH patients from the Phase 3 trial APL2-302.

Table 1: Summary of Anti–Pegcetacoplan Peptide Antibody (ADA) Screening and Confirmation Results

Clinical study	Study APL2-302 (Pegasus) RCP, OLP, Follow-up	Study 204 (Paddock)	Study 202 (Palomino)	Study 101 (multiple SC dose)	Study 205 (renal impairment study)	Study 102 (healthy Japanese study)
Healthy Subjects or Disease diagnosis	PNH	PNH	PNH	Healthy	Healthy and renal impairment	Healthy Japanese
Total subjects enrolled in the study	80	17	4	40	16	20
Number (%) of subjects screened positive (ie, tested positive by the Screening Assay at any visit)	37 (46.3)	7 (41.2)	0 (0)	8 (20)	2 (12.5)	1 (5.0)
Number (%) of subjects confirmed positive for ADA	2 (2.5)	2 (11.8)	0 (0)	3 (7.5)	1 (6.3)	0 (0)
Time point for confirmed positive ADA	Week 16, Week 16	Day 1 predose; Day 1 predose	NA	Day 84, Day 84, Day 1 pre-dose	Day 1 predose	NA
Nature of ADA	Treatment-emergent	Pre-existing	NA	2 Treatment-emergent; 1 pre-existing	Pre-existing	NA
Number (%) of subjects screened positive, but not confirmed positive for ADA	35 (43.8)	5 (29.4)	NA	5 (12.5)	1 (6.3)	1 (5.0)
Number (%) of subjects with treatment-emergent response	2 (2.5)	0 (0)	0 (0)	2 (5.0)	0 (0)	0 (0)
Number (%) of subjects with treatment-boosted response	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total samples analysed for ADA	486	177	35	166[a]	32	39
Titers of ADA for all positive results	1:10, 1:10	1:10, 1:10	NA	<1:10, 1:10, 1:10	1:40	NA
Number (%) of samples screened positive (ie, tested positive by the Screening Assay at any visit)	91 (18.7)	37 (20.9)	0 (0)	12 (7.2)	2 (6.3)	2 (5.1)
Number (%) of samples tested positive by the confirmation assay	2 (0.4)	2 (1.1)	0 (0)	3 (1.8)	1 (3.1)	0 (0)

[a] A follow-up sample was tested after submission of Module 2.7.2 (reflected in amended bioanalytical report BAL-19-143-073). This increased total samples analysed from 165 to 166.

Table 2: Summary of Anti–PEG Antibody (ADA) Screening and Confirmation Results

Clinical study	Study APL2-302 (Pegasus) RCP, OLP, Follow-up	Study 204 (Paddock)	Study 202 (Palomino)	Study 101 (multiple SC dose)	Study 205 (renal impairment study)	Study 102 (healthy Japanese study)
Healthy Subjects or Disease diagnosis	PNH	PNH	PNH	Healthy	Healthy and renal impairment	Healthy Japanese
Total subjects enrolled in the study	80	17	4	40	16	20
Number (%) of subjects screened positive (ie, tested positive by the Screening Assay at any visit)	69 (86.3)	14 (82.4)	1 (25)	35 (87.5)	14 (87.5)	19 (95.0)
Number (%) of subjects confirmed positive for ADA	68 (85.0)	13 (76.5)	1 (25)	34 (85)	13 (81.3)	17 (85.0)
Time point for confirmed positive ADA	Week -4, -3, 1, 16, 32, 48, 54, 60	Day 1,15,29,71,141 ,197,253,309,3 65,421,477	Day 15, 29	Day 1,8,15,22,25,2 9,35,42,56,70, 84	Day 1, 5, 15, 29, 43	Day 1, 5, 8, 15, 22, 29, 43
Nature of ADA	Pre-existing, treatment-emergent and treatment-boosted	Pre-existing, treatment-emergent and treatment-boosted	Treatment-emergent	Pre-existing, treatment-emergent and treatment-boosted	Pre-existing, Treatment-boosted	Pre-existing, treatment-emergent
Number (%) of subjects screened positive, but not confirmed positive for ADA	1 (1.25)	1 (5.9)	0 (0)	1 (2.5)	1 (6.3)	2 (10.0)
Number (%) of subjects with treatment-emergent response	2 (2.5)	2 (11.8)	1 (25)	2 (5.0)	0 (0)	2 (10)
Number (%) of subjects with treatment-boosted response	4 (5.0)	3 (17.6)	0 (0)	1 (2.5)	1 (6.3)	0 (0)
Titers of ADA for all positive results	1:10 to 1:20500	1:10 to 1: 2560	1:80 to 1:160	1:10 to 1:10240	1:10 to 1:160	1:10 to 1:1280
Total samples analysed for anti-PEG antibody	486	178	35	172	35	48
Number (%) of samples screened positive (ie, tested positive by the Screening Assay at any visit)	266 (54.7%)	74 (41.6)	2 (5.7)	141 (82.0)	29 (82.9)	42 (87.5)
Number (%) of samples tested positive by the confirmation assay	239 (49.2)	72 (40.4)	2 (5.7)	127 (73.8)	28 (80.0)	37 (77.1)

Regarding the incidence of anti-pegcetacoplan peptide antibodies in Table 1, you stated that "As expected, the number (%) of subjects or samples screened positive is higher than those confirmed positive, reflecting higher specificity of the confirmation assay". However, since the CCP for the anti-pegcetacoplan peptide antibody assay is quite high (>50% reduction in binding), the higher % of screened positive subjects (and samples) as compared to those confirmed positive may reflect an underestimation of true positives by the confirmatory assay. Indeed, the anti-PEG antibody assay in which CCP and the LPC response did not raise concerns generated percentages of screened positive subjects (and samples) quite similar to those for confirmed positives. It was also stated that "Based on careful evaluation of all the data, including data beyond Week 16 of Study APL2-302 and those from healthy volunteer studies, and within the context of the assay limitation on drug tolerance, it is concluded that anti–pegcetacoplan peptide antibodies occur infrequently, and when they do, it is at low titers (at most 1:10 for all observed incidences of treatment-emergent anti-pegcetacoplan antibody responses)". However, it may be possible that on-board drug interference may lead to an underestimation of true positive samples and also impact on the titer assessment.

A summary of principles and results of NAb assay formats tested during development was provided. The format you have validated is adequate. However, as for the anti-pegcetacoplan peptide assay, the interference of on-board drug with the NAb assay performance remains a concern.

Thank you for specifying the location of data on CP determination, sensitivity and precision for the NAb assay. Data in Validation Report no. BAL-17-143-027-REP are reviewed below. NAb assay precision of in-study runs (Table 7, report no. BAL-20-503-011-REP) appears acceptable, however, raw data could not be located in the submission. The CP for anti-pegcetacoplan peptide and anti-PEG antibody assays should be confirmed or re-established using pre-dose samples from the patient population prior to testing pivotal study samples. If CP are re-established, sensitivity should be re-evaluated accordingly. The precision of ADA assay runs with pivotal study samples should also be evaluated and reported using precision data for the controls tested on the same plates of study samples.

The Assessors concluded that your ADA assays developed to detect antibodies directed against the functional peptide of pegcetacoplan and their neutralizing ability have a low drug tolerance and circulating drug levels in clinical samples may interfere with their performance.

To adequately assess the immunogenicity risk for pegcetacoplan, the following PMC were requested and accepted by the sponsor:

1) 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 anti-Pegcetacoplan 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.
2) PMC 2: Develop and validate a sensitive assay to evaluate the neutralizing activity of anti-Pegcetacoplan antibodies (ADA) detected in patient samples. The assay should be capable of sensitively detect 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.
3) 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.

The rationale behind these PMC is to 1) render improved immunogenicity assays to confirm the presence of ADA and their neutralizing ability in clinal study samples in the presence of circulating drug and 2) collect additional immunogenicity data from Phase 3 clinical trials. Together, this is to allow a more adequate assessment of the incidence of ADA in pegcetacoplan-treated subjects and subsequent impact of ADA on PK, PD, safety, or effectiveness of pegcetacoplan product.

Review of ADA and NAb assays

- Unless otherwise noted, figures and tables in this review are copied directly from the submission.
- The review sequence of the individual aspect of the assay validation may not follow the exact sequence in the submission.
- The "guidance" cited in the review refers to the "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
- The Assessor's comments are shown in italic font.

Validation of Anti-Drug Antibody Assay

During development, a direct ELISA-based ADA assay was used to test immunogenicity samples from early clinical studies for ADA to the whole molecule of pegcetacoplan. In this assay, human serum samples are incubated with pegcetacoplan immobilized on an ELISA plate. After washing, the bound antibodies are detected by using goat anti-human IgG/A/M-HRP antibodies (rabbit anti-mouse IgG-HRP for the mouse anti-PEG positive control) and the TMB substrate solution as detection reagent. The colorimetric signal is measured at 450 nm (with a 650-nm wavelength correction) by plate reader.

Later during development, ADA assays specific for antibodies against the peptide moiety of pegcetacoplan (Anti-Pegcetacoplan Peptide Antibody Assay) or the PEG moiety of pegcetacoplan (Anti-PEG Antibody Assay) were developed and used to test immunogenicity samples from the Phase 3 study APL2-302.
The Anti-Pegcetacoplan Peptide Antibody Assay and the Anti-PEG Antibody Assay used in Phase 3 Safety and reviewed below follow a multi-tiered testing strategy. Serum samples are first tested in an ADA screening assay and those screened positives are subsequently tested in a confirmatory assay. Confirmed positive samples are tested for titer.

- **Method Principle**

  Anti-Pegcetacoplan Peptide Antibody Assay:

This is a Meso Scale Discovery-Based (MSD) Electrochemiluminescence (ECL) assay. In brief, for both the screening and titer assays, streptavidin-coated magnetic beads are incubated with biotinylated PEG, washed and resuspended in blocking buffer. Diluted samples and controls are then combined with the beads in a 96-well polypropylene plate for overnight (O/N) incubation at 4°C while shaking. After O/N incubation, the plate is brought to RT and placed on a magnet to recover supernatants from beads that captured anti-PEG antibodies. Supernatants are subsequently transferred to appropriate wells of an MSD plate coated with pegcetacoplan, human IgG, or human IgM. After washing, ADA are detected with an antibody cocktail (anti-mouse-rabbit IgG-ruthenium, anti-human IgM-ruthenium, and anti-human IgG-ruthenium) and Read Buffer T. The plate is read on MSD Imager 600 Reader.
The confirmatory assay procedure is the same with the exception that samples and controls are diluted to the MRD in buffer containing 4 µg/mL of pegcetacoplan.

Anti-PEG Antibody Assay:
This is an ELISA. In brief, for both the screening and titer assays, streptavidin-coated magnetic beads are incubated with biotinylated PEG. Diluted samples are then combined with the beads in a 96-well polypropylene plate for O/N incubation at 4°C while shaking. After O/N incubation, the plate is placed on a magnet to remove supernatants and collect beads that captured anti-PEG antibodies. Anti-PEG antibodies are dissociated from the beads with acetic acid, on a magnet. Tris buffer was used to neutralize the acidified samples. The neutralized samples containing any anti-PEG antibodies and controls are subsequently added to appropriate wells of a Maxisorp plate coated with multi-PEGylated BSA or control human Ig. After washing, ADA are detected with an antibody cocktail (goat anti-mouse IgG-HRP and goat anti-human IgG-HRP) and TMB substrate solution as detection reagent. The colorimetric signal is measured at 450 nm by plate reader.
The confirmatory assay procedure is the same with the exception that samples and controls are diluted to the MRD in buffer containing 400 µg/mL of 40-kDa PEG.

Assessor's Comment:
The Applicant's strategy to evaluate ADA specific for the peptide moiety or the PEG moiety of pegcetacoplan in human serum samples is adequate. However, there are concerns that for the anti-pegcetacoplan peptide antibody assay, LPC and CCP may not have been set correctly and that the presence of circulating drug may interfere with the detection of ADA. The assay acceptance criteria should be re-evaluated based on the Assessor's comments in the table below.

- ***Validation Results and Assessor Analysis for ADA Assays Used in Phase 3 Safety (Validation Reports: BAL-17-143-048-REP for Anti-Pegcetacoplan Peptide Antibody Assay; BAL-17-143-050-REP for Anti-PEG Antibody Assay)***

Validation Parameter	Clin Study APL2-302 Validation Report No. BAL-17-143-048-REP	Clin Study APL2-302 Validation Report No. BAL-17-143-050-REP	Assessor Comment
Contract Research Organization	(b) (4)	(b) (4)	*N/A*

Assay principle	ECL assay for the detection of antibodies against pegcetacoplan peptide in human serum	ELISA for the detection of antibodies against PEG in human serum	*The proposed assays detect only IgG, IgM ADA isotypes*
Sample Pretreatment (Acid dissociation, beads…)	Samples are pretreated with streptavidin-coated magnetic beads incubated with biotinylated PEG to separate supernatants for downstream analysis from beads that captured anti-PEG antibodies	Samples are pretreated with streptavidin-coated magnetic beads incubated with biotinylated PEG, followed by acid dissociation to extract anti-PEG antibodies	*Acceptable*
Positive control (PC)	Rabbit polyclonal antibody directed against the functional moiety of pegcetacoplan Additional controls: Human IgG and IgM coated wells for detection controls	Mouse anti-PEG monoclonal antibody Additional controls: • Human anti-PEG controls prepared by diluting in NC serum a human sample with high anti-PEG response; • Human IgG and IgM coated wells for detection controls	*Acceptable* *During validation each plate included at least one set (in duplicate) of PCs*
PC Dose Curve and Hook Effect	No hook effect detected up to 125,000 ng/mL PC	No hook effect detected up to 5000 ng/mL PC	*N/A*
LPC	35 ng/mL	50 ng/mL	*In the Anti-Pegcetacoplan Peptide Antibody Assay, LPC may not have been set correctly (see also comments below for CCP and assay acceptance criteria).* *LPC2 is acceptable*
LPC2	N/A	25 ng/mL	
MPC	500 ng/mL	200 ng/mL	*N/A*
HPC	2500 ng/mL	500 ng/mL	*Acceptable*
Matrix and NC	Pooled normal human serum (NHS)	Pooled normal human serum (NHS). Sera were pre-screened to include in the matrix and NC those	*Acceptable.* *Since normal human sera may contain antibodies to PEG, the approach of using in the anti-PEG*

		with lowest anti-PEG responses	*antibody assay a matrix of preselected sera is adequate.* *This approach was not necessary for the anti-pegcetacoplan peptide antibody assay because samples, including controls, are pretreated with beads to remove anti-PEG antibodies.* *During validation each plate included three sets (in duplicate) of NC*
MRD	1:10	1:10	*N/A*
Screening cut-point (SCP)	Determined from 64 individual NHS. Sera were tested in duplicate by 2 analysts over three independent assay runs per analyst, resulting in 6 datasets. • Datasets: log-transformed normalized ECL signal values (Mean ECL signal of sample/Mean ECL signal of NC on the same assay plate); • Data exclusion: 22 values were excluded prior to log-transformation because had a %CV > 25%. Of the remaining log-transformed normalized values, 10 were found to be analytical outliers and excluded after 5 iterations. 6 additional values were also removed because from 1	Determined from 56 individual NHS. Sera were tested in duplicate by 2 analysts over three independent assay runs per analyst, resulting in 6 datasets. Since normal human sera may have pre-existing antibodies to PEG, the 56 lots were arbitrarily divided into 2 groups: 1) a group of 15 lots, which yielded low screening and confirmatory results and 2) a group with a larger dataset comprising the remaining 41 lots. The latter group was chosen, outliers were excluded, and the distribution of each dataset within the group was analyzed for SCP determination as described below. • Datasets: log-transformed normalized	*The SCP determined using normal human sera are acceptable. LPC of assay runs ≥ SCP.* *The in-study CP should be confirmed or re-evaluated using pre-dose samples of the patient population.* *Data and statistical analysis for the in-study CP determination could not be located or were not provided*

	lot identified as a biological outlier; • Criteria for outlier exclusion: Above 75th percentile + (1.5 × IQR). Below 25th percentile – (1.5 × IQR); • Distribution after outlier removal: normal for 5 of the 6 datasets using the S-W test; • Method: 95% quantiles from each dataset were used, back-transformed to non-log normalized values, and then averaged to obtain a SCP targeting a 5% false positive rate; • SCP: 1.96 normalized ECL signal value	signal values (Mean OD of sample/Mean OD of NC on the same assay plate); • Outlier exclusion: 8 analytical outliers were excluded after 3 iterations. No biological outliers were found; • Criteria for outlier exclusion: Above 75th percentile + (1.5 × IQR). Below 25th percentile – (1.5 × IQR); • Distribution after outlier removal: non-normal for all 6 datasets using the S-W test; • Method: 5% quantiles from each dataset were used and averaged to obtain the SCP; • SCP: 1.41 normalized signal value	
Confirmatory cut-point (CCP)	Determined using the same datasets and criteria for outlier exclusion as for the SCP but using % inhibition values. • Datasets: % Inhibition values [(1-(Signal of spiked sample/Signal of corresponding unspiked sample)) x 100]; • Outlier exclusion: 9 analytical outliers; • Distribution after outlier removal: normal with S-W test p value = 0.0693; • Method: 99% quantile was used to obtain a CCP	Determined using the same group with the larger dataset from 41 NHS and criteria for outlier exclusion as for the SCP but using % inhibition values. • Datasets: % Inhibition values [(1-(Signal of spiked sample/Signal of corresponding unspiked sample)) x 100]; • Outlier exclusion: No outliers were found; • Distribution after outlier removal: non-normal with S-W test p value < 0.0001;	*The CCP for the anti-pegcetacoplan peptide antibody assay, determined using normal human sera, is high and may not have been set correctly. 22% of LPC scored below the CCP in confirmatory assay runs used to assess precision. The high CCP does not appear to be the result of high assay variability.* *The CCP for the anti-PEG antibody assay is acceptable. All LPC scored above the CCP in*

	targeting a 1% false positive rate; • CCP: 50.3 % inhibition	• Method: 1% quantile was used to obtain the CCP; • CCP: 32.2 % inhibition	*confirmatory assay runs used to assess precision*
Titer Cut Point (TCP)	Same as SCP Final titer values are reported as the last dilution fold generating a signal above the TCP x MRD	Same as SCP Final titer values are reported as the last dilution fold generating a signal above the TCP x MRD	*Same comments as for the SCP.* *Final titer value determination is acceptable*
Sensitivity	Sensitivity (in neat matrix) of screening and confirmatory assays was determined by interpolating 3 PC dilution curves to SCP and CCP, respectively. Results from the 3 curves were averaged and the sensitivity was set at 19.9 ng/mL for screening assay and 17.0 ng/mL for confirmatory assay	Sensitivity (in neat matrix) of screening and confirmatory assays was determined by interpolating 6 PC dilution curves to SCP and CCP, respectively. Results from the 6 curves were averaged and the sensitivity was set at 9.06 ng/mL for screening assay and 9.74 ng/mL for confirmatory assay	*The approach used to determine the sensitivity of screening and confirmatory assays is acceptable. Assay sensitivity should be re-evaluated if CP for the in-study analysis are re-established*
Assay Drug tolerance	HPC, MPC, and LPC tolerated up to 500, 62.5, and 0.244 µg/mL of on-board pegcetacoplan, respectively	HPC and MPC tolerated up to 5 mg/mL of on-board drug, while the LPC2 tolerated 625 µg/mL	*This product raises concerns about on-board drug interference with anti-pegcetacoplan peptide antibody detection as 1) the drug's half-life in PNH subjects (given twice a week at a sc dose of 1080 mg) was estimated to be 8 days and 2) steady-state serum drug concentrations (after 2 weeks of dosing) were greater than 600 µg/mL. Approaches to increase drug tolerance of the anti-pegcetacoplan peptide*

			antibody assay should be considered. *Drug tolerance for the anti-PEG antibody assay is acceptable. This assay includes sample pretreatment steps with beads and acid buffer to extract anti-PEG antibodies*
Precision	• Screening assay: Inter-assay precision was assessed using control data from 20 runs (Passing runs). Data from 3 runs (Failed runs) were excluded from the analysis because positive controls did not meet acceptance criteria. When considering "Passing run" data for inter-assay precision, %CV of normalized signal values for LPC = 18.5%, MPC = 24.2%, and HPC = 21%; NC < 15%. For intra-assay precision, %CV of all controls < 20%. • Confirmatory assay: Inter-assay precision was assessed using control data from 9 runs (Passing runs). Data from 2 runs (Failed runs) were excluded from the analysis because positive controls did not meet acceptance criteria. When considering	• Screening assay: Inter-assay precision was assessed using control data from 18 runs. %CV of normalized signal values for HPC and MPC mouse antibodies < 25%; the other controls had a %CV < 20%. For intra-assay precision, %CV of all controls ≤ 12%. • Confirmatory assay: Inter-assay precision was assessed using control data from 10 runs. %CV < 10% For intra-assay precision, %CV < 10%	*HPC and MPC in both anti-pegcetacoplan peptide antibody assays and anti-PEG antibody assays had %CV for inter-assay precision up to 24-25%.* *According to the guidance, the target acceptance criteria for assay precision should be set as %CV < 20%*

	"Passing run" data for inter-assay precision, %CV of controls ≤ 20%		
Selectivity	10 NHS were spiked with LPC and HPC in two runs tested by two different analysts, generating 40 spiked samples. All, but 4 (2 LPC and 2 HPC spiked samples, attributed to a technical error), scored positive in the screening assay	10 NHS spiked with LPC and HPC, all scored positive in the screening assay	*Acceptable*
Stability	LPC and HPC were spiked into pooled NHS and frozen for at least 24h prior to thawing and screening assay analysis. • For short-term stability thawed samples were kept for approx. 4h at RT or approx. 23h at 2-8°C; • For freeze-thaw cycle analysis, stability of LPC and HPC was evaluated after 6 and 9 cycles (-80C/RT). All PCs yielded results above the SCP	• For short-term stability, LPC and HPC were kept for 25h at RT and 30 min at 2-8°C; • For freeze-thaw cycle analysis, stability of LPC and HPC was evaluated after 6 and 9 cycles (-80C/RT); • Stability of beads conjugated with biotin-PEG and stored at 2-8°C for 26 days was also evaluated All PCs yielded results above the SCP	*PCs in the stability runs yielded positive results within the range of values obtained in other runs. Assay runs were conducted using previously frozen PCs. % recoveries compared to freshly prepared samples were not evaluated*
Lipemia	100% to 0% lipemic pooled NHS samples were spiked with LPC. All scored positive in the screening assay and increased lipemia levels did not interfere with the PC detection	100% to 0% lipemic pooled NHS samples were spiked with LPC. All scored above the SCP. Lipemia did not interfere with the PC detection	*Acceptable*
Hemolysis	100% to 0% hemolyzed pooled NHS samples were spiked with LPC. All scored positive in the screening	100% to 0% hemolyzed pooled NHS samples were spiked with LPC. All scored above the SCP.	*Acceptable*

	assay. Hemolysis did not interfere with the PC detection	Hemolysis did not interfere with the PC detection	
Assay Acceptance Criteria	All replicate measurements: %CV ≤ 25% NC < CP HPC > LPC ≥ CP	Replicate measurements in sensitivity and selectivity runs: %CV ≤ 20% Inter-assay and intra-assay precision: %CV ≤ 25% NC < CP HPC > LPC > CP	*Target acceptance criteria for assay precision should be set at %CV < 20%. Acceptance ranges for LPC and HPC readouts in screening and confirmatory assays could not be located or were not provided. Acceptance criteria for PC readouts as HPC > LPC > CP are not recommended.* *For the anti-Pegcetacoplan Peptide Antibody Assay, 22% of LPC scored below the CCP in confirmatory assay runs used to assess precision (Table 21, Validation Report No. BAL-17-143-048-REP)*

Validation of Neutralizing Anti-Drug Antibody Assay

The NAb assay is an ECL-based competitive ligand-binding assay and detects pegcetacoplan NAbs in human serum

- **Method Principle**

  In brief, samples are first exposed to a protein A/G/L sepharose column to separate most Ig, including potential NAbs, from serum containing high circulating concentration of complement C3, then eluted from the column with an acid solution, neutralized with Tris buffer, and transferred on a MSD plate coated with 0.125 µg/mL of pegcetacoplan. If present, NAbs bind to pegcetacoplan, competing with a sulfo-tagged human complement C3 (the target of pegcetacoplan). More NAbs, less sulfo-tagged human complement C3 captured by the coated pegcetacoplan, and less ECL signal produced.

Assessor's Comment:
Since this assay measures the binding activity of pegcetacoplan to the human complement C3, which reflects the MOA of the drug product, its format is appropriate for evaluating the interference with this activity of neutralizing anti-pegcetacoplan antibodies.
However, there is concern that the on-board drug may interfere with the performance of the assay. Furthermore, selectivity and domain specificity for the functional moiety of the drug were not evaluated at LPC concentrations.

- ***Validation Results and Assessor Analysis for Neutralizing ADA assay (Validation Report No. BAL-17-143-027-REP)***

Validation Parameter	Validation Report No. BAL-17-143-027-REP	Assessor Comment
Contract Research Organization	(b) (4)	*N/A*
Assay principle	ECL-based competitive ligand-binding assay for the evaluation of neutralizing antibodies against pegcetacoplan in human serum samples	*This assay is designed to detect neutralizing ADA in human serum samples, despite the presence of complement C3, the target of pegcetacoplan. This assay also detects most Ig*
Sample Pretreatment (Acid dissociation, beads…)	Samples are exposed to a protein A/G/L sepharose column to separate potential NAbs from serum containing circulating complement C3, which can interfere with the assay performance. Antibodies are eluted from the column with an acid solution	*Acceptable*
Positive control (PC)	Affinity purified rabbit anti-pegcetacoplan peptide antibody	*Acceptable.* *Each plate included 2 sets of PCs*
PC Dose Curve and Hook Effect	Not provided	
LPC2	443 ng/mL	*Acceptable.*
LPC1	523 ng/mL	*LPC1 was initially used during validation.* *LPC2 was established after CP and sensitivity determination during validation and set based on*

		sensitivity data to fail in 1% of the runs. *LPC2 will be used during testing of clinical samples*
MPC	1306 ng/mL	*N/A*
HPC	3919 ng/mL	*Acceptable*
Matrix and NC	Pooled normal human serum	
MRD	1:4	*N/A*
Cut-point (CP)	Determined from serum of 50 drug naïve individuals. Sera were tested in duplicate by 2 analysts over three independent assay runs per analyst, resulting in 6 datasets. • Datasets: log-transformed normalized ECL signal values (Mean ECL signal of sample/Mean ECL signal of NC on the same assay plate); • Data exclusion: 7 values were excluded prior to log-transformation because had a %CV > 20%. Of the remaining log-transformed normalized values, 24 were found to be analytical outliers and excluded. 6 additional values were also removed because from 2 individual biological outliers; • Criteria for outlier exclusion: Above 75th percentile + (1.5 × IQR). Below 25th percentile – (1.5 × IQR); • Distribution after outlier removal: non-normal with S-W test p value < 0.0001 and skewness = 1.70; • Method: 1% quantile estimate, back-transformed to non-log value, was used to obtain a CP targeting a 1% false positive rate; • NAb assay CP: 0.867 normalized ECL signal value	*The CP determined during validation is acceptable. LPC < CP* *The in-study performance of the assay, including CP, can not be assessed because NAb results in the clinical setting were not provided*
Sensitivity	Sensitivity (in neat matrix) was determined by interpolating 12 PC dilution curves to the CP. Results from all titration curves were averaged and the sensitivity was set at 288 ng/mL	*The assay sensitivity is greater than 100 ng/mL, but acceptable for a NAb assay.*

		Assay sensitivity should be re-evaluated if CP for the in-study analysis is re-established
Assay Drug tolerance	HPC tolerated up to 10 µg/mL of on-board drug, while the LPC2 did not tolerate 400 ng/mL (lowest drug concentration tested)	*Although the assay includes steps to extract Ig (including NAbs), these levels of drug tolerance raise a concern for on-board drug interference with the performance of the NAb assay (see also comment about drug tolerance for the anti-pegcetacoplan peptide antibody assay)*
Precision	6 runs by two analysts. For intra- and inter-assay, %CV of LPC1, LPC2, MPC, HPC, and NC all < 20%	*Acceptable*
Selectivity	10 serum samples spiked with HPC (3919 ng/mL) and the PC at a lower concentration (1210 ng/mL), all tested positive	*Acceptable at concentration levels of HPC and near the MPC.* *Matrix interference at the LPC1 and LPC2 concentrations was not evaluated*
Specificity	Specificity of the assay to detect NAbs against pegcetacoplan peptide (the functional moiety of the drug) was evaluated by spiking 40K-PEG at concentrations of 10 and 100 µg/mL into 3000 ng/mL PC. Samples tested positive	*Acceptable at concentration of PC near the HPC.* *Domain specificity at the LPC1 and LPC2 concentrations was not evaluated*
Robustness	HPC, MPC, LPC1, LPC2, and NC were tested under various incubation times	*Acceptable.* *PC samples tested positive; NC > CP ≥ LPC > MPC > HPC*
Stability	• For short-term stability, LPC2 and HPC were kept for approx. 40h at RT and 2-8°C; • For freeze-thaw cycle analysis, stability of LPC2 and HPC was evaluated after 6 and 9 cycles (-80C/RT)	*PCs yielded positive results with normalized mean ECL values < CP* *% recoveries compared to freshly prepared samples were not evaluated*
Lipemia	3 lipemic sera tested unspiked or spiked with HPC (3919 ng/mL) and the PC at a lower concentration (1210 ng/mL).	*The Applicant stated that "visibly lipemic samples will not be run without additional testing of lipemic samples"*

	Unspiked lipemic samples tested negative (normalized ECL signal > CP), while those spiked with PC tested positive (normalized ECL signal < CP), but with high %CV. Lipemia interfered with PC detection	
Hemolysis	3 hemolyzed serum spiked with HPC (3919 ng/mL) and the PC at a lower concentration (1210 ng/mL). Unspiked hemolytic samples tested positive (normalized ECL signal < CP), but those spiked with PC tested more positive in a dose dependent manner (normal. signal spiked samples < normal. signal unspiked samples < CP). Hemolysis may yield false positive results	*The Applican stated that "hemolysis did not inhibit the ability of the assay to detect positive samples and hemolytic samples can be tested"*
Assay Acceptance Criteria	All replicate measurements: %CV ≤ 20% HPC < LPC < CP NC > LPC > MPC > HPC	*Acceptance ranges for LPC and HPC readouts could not be located or were not provided. Acceptance criteria for PC readouts as HPC < LPC < CP are not recommended*

Assessment of Assay performance in Clinical Studies

Assessor's Comment:

The ADA assay performance in Phase 3 clinical study could not be assessed because data for 1) the in-study CP determination and 2) the in-study sensitivity, selectivity and precision could not be located or not provided.

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/s/

MARCO CARDONE
05/10/2021 05:48:13 PM

DANIELA I VERTHELYI
05/10/2021 09:18:01 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 3, 2021
Requesting Office or Division:	Division of Nonmalignant Hematology (DNH)
Application Type and Number:	NDA 215014
Product Name and Strength:	Empaveli (pegcetacoplan) injection 1,080 mg/20 mL (54 mg/mL)
Applicant/Sponsor Name:	Apellis Pharmaceuticals, Inc. (Apellis)
FDA Received Date:	April 20, 2021
OSE RCM #:	2020-1939-1
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Apellis submitted a revised container label and carton labeling for Empaveli (pegcetacoplan) injection on April 20, 2021 (Appendix A). The revisions are in response to recommendations that we made during a previous label and labeling review[a] and via a labeling communication email[b]. We reviewed the revised labels and labeling to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

We note that all previous recommendations were implemented. We conclude the revised container label and carton labeling are acceptable from a medication error perspective. We have no additional recommendations at this time.

[a] DeGraw, S. Label and Labeling Review for Empaveli (pegcetacoplan) NDA 215014. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 12. RCM No.: 2020-1939.
[b] Thompson, C. Email: NDA 215014 Labeling Communication Email. 2021 APR 14. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80596ee0

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/s/

STEPHANIE L DEGRAW
05/03/2021 03:30:12 PM

HINA S MEHTA
05/04/2021 03:17:23 PM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)

Date:	April 29th, 2021
DEPI-1 Reviewer:	Steven Bird, PhD, PharmD, MS
DEPI-1 Division Director:	Simone Pinheiro, ScD, MSc
OPE Deputy Director:	Michael Blum, MD, MPH
FDA Sentinel Team Lead:	Michael D. Nguyen, MD
OSE Deputy Director:	Robert Ball, MD, MPH, ScM
Subject:	ARIA Sufficiency Memo
Drug Name(s):	Pegcetacoplan
Application Type/Number:	NDA-215014
Applicant/sponsor:	Apellis Pharmaceuticals Inc
OSE RCM #:	2021-159

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X

	Serious Infections	**Autoimmune Disease**
Surveillance or Study Population		
Exposure		
Outcome(s) of Interest	X	X
Covariate(s) of Interest	X	
Surveillance Design/Analytic Tools		

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Pegcetacoplan is a PEGylated 40kDa polyethylene glycol linear small molecule that acts as a C3 complement inhibitor. The dosage is 1080mg subcutaneously twice weekly. The Applicant submitted a Biological Licensing Application (BLA) for pegcetacoplan for the proposed indication of the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). PNH is a rare acquired genetic disorder of a bone marrow stem cell with an estimated incidence of 1 to 10 cases per million population. The median age of onset is 35 to 40 years. Classical PNH is characterized by complement mediated intravascular hemolytic anemia, bone marrow failure, and atypical thromboses. Standard of care includes allogeneic hematopoietic cell transplantation and complement inhibition with intravenous eculizumab.

1.2. Describe the Safety Concern

The Applicant has proposed a boxed warning to include serious infections caused by encapsulated bacteria. The mechanism of action of pegcetacoplan provides proximal inhibition of the complement system which creates a higher risk of serious infections caused by encapsulated bacteria, including *Streptococcus pneumoniae, Haemophilus influenzae* and *Neisseria meningitidis*. These associations are based on the review of manifestations of inherited C3 complement deficiencies, which have shown recurrent and severe infections involving the respiratory system, meninges, and blood stream caused by the above mentioned encapsulated bacterial organisms. These infections are serious, life-threatening, often requiring hospitalization and significant medical management, as well as, potentially fatal (Risitano, 2017; Figeroa, 1991). 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 *Neisseria meningitidis* infections (Ram, 2010).

There were however no infections due to encapsulated bacteria observed in the phase III randomized clinical trial (RCT) under review by FDA. Still, there is a potential risk of serious infections with encapsulated bacteria due to the mechanism of action of pegcetacoplan, as with all complement therapies. Infections overall were observed in 12 of 41 (29%) patients receiving pegcetacoplan and 10 of 39 (26%) patients receiving ecluzimab in the phase III RCT. Additional data are needed to characterize the risk and the incidence rate of serious infections overall, and those due to encapsulated bacterial infections, leading the FDA to seek further study post-approval.

Additionally, the literature has shown that there is a theoretical increased risk of autoimmune disease, including systemic lupus erythematosus (SLE) development in patients with C3 deficiency. Therefore, it is important for the understanding of the safety of the drug to monitor patients long-term to determine if this is observed in patients receiving pegcetacoplan (Schroder-Braunstein, 2019; Sturfelt, 2005).

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

	Serious Infections	Autoimmune Diseases
Assess a known serious risk	X	
Assess signals of serious risk		
Identify unexpected serious risk when available data indicate potential for serious risk		X

1.4. Statement of Purpose

The purpose of this analysis is to provide a descriptive characterization of the patient experience with pegcetacoplan. It will describe serious infections during follow-up, including those caused by encapsulated bacteria, in addition to development of autoimmune diseases.

1.5. Effect Size of Interest or Estimated Sample Size Desired

This study will have a goal for collection of data on 200 patients.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The desired population consists of patients with paroxysmal nocturnal hemoglobinuria (PNH).

2.2 Is ARIA sufficient to assess the intended population?

Because PNH will be the only indication for this drug after its initial approval, the exposure itself should be adequate to identify the intended population.

3 EXPOSURES

3.1 Treatment Exposure(s)

The exposure is use of pegcetacoplan.

3.2 Comparator Exposure(s)

Not applicable.

3.3 Is ARIA sufficient to identify the exposure of interest?

Pegcetacoplan is expected to be identifiable through injection procedures codes post approval.

4 OUTCOME(S)

4.1 Outcomes of Interest

The first outcome of interest is serious infections overall and those caused by encapsulated bacteria.

The second outcome of interest is autoimmune diseases, including but not limited to systemic lupus erythematosus (SLE).

4.2 Is ARIA sufficient to assess the outcome of interest?

ARIA has algorithms to identify serious infections. However, available algorithms do not have sufficient capacity to characterize infections as due to encapsulated bacteria. Because identification of encapsulated bacterial infections is critical to this study, ARIA is not sufficient for this outcome.

Diagnostic codes are available for many autoimmune diseases. Diagnostic and treatment coding could be combined to identify many of them. Given the large number of autoimmune diseases and insufficiencies elsewhere in this memo, a comprehensive review of coding for autoimmune diseases was not conducted. Overall, the large number of autoimmune diseases makes this a highly challenging outcome to study in ARIA, and it is likely ARIA would not have sufficient sensitivity for identification of this outcome. Also, there is a desire to monitor patients for 5 years after treatment initiation, making post-index observation time a limitation of ARIA. Thus, ARIA is also insufficient for autoimmune diseases.

5 COVARIATES

5.1 Covariates of Interest

Due to the increased risk of serious encapsulated bacteria, one would need the complete vaccination status for all patients receiving pegcetacoplan, with particular emphasis on meningococcal and pneumococcal vaccines. Additionally, it is important to know if these patients are not fully vaccinated against encapsulated bacteria, and if they are receiving prophylactic antibiotic therapy while receiving pegcetacoplan.

5.2 Is ARIA sufficient to assess the covariates of interest?

ARIA is not sufficient. Vaccination history is a key component for understanding serious risk of infections, and this cannot be accurately obtained with just a 1-year lookback period prior to starting pegcetacoplan therapy.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

The intended study design is an observational patient registry with descriptive data analysis.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

The desired observational registry requires only descriptive statistics. The analytic tools within Sentinel are not a limiting factor.

7 NEXT STEPS

A PMR will be issued for an observational registry with primary data collection. The study design will ensure long term follow up to a minimum of 5 years after initial exposure to detect autoimmune diseases and other long latency safety outcomes.

The PMR language is below:

"*Establish a registry to characterize the long-term safety of pegcetacoplan in adult patients with paroxysmal nocturnal hemoglobinuria (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 (SLE) 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.*"

8 REFERENCES

1) Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. *Clin Microbiol Rev*. 1991 Jul;4(3):359-95.
2) Ram S, Lewis LA, Rice PA. Infections of people with complement deficiencies and patients who have undergone splenectomy. *Clin Microbiol Rev*. 2010;23(4):740-780.
3) Risitano AM, Ricklin D, Huang Y, et al. Peptide inhibitors of C3 activation as a novel strategy of complement inhibition for the treatment of paroxysmal nocturnal hemoglobinuria. *Blood*. 2014; 123(13):2094-2101.
4) Schroder-Braunstein J, Kirshfink M. Complement deficiencies and dysregulation: Pathophysiological consequences, modern analysis, and clinical management. *Mol Immunol.* 2019; 114:299-311.
5) Sturfelt G, Truedsson L. Complement and its breakdown products in SLE. *Rheumatology*. 2005; 44:1227-1232.

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/s/

STEVEN BIRD
04/29/2021 12:53:32 PM

SIMONE P PINHEIRO
04/29/2021 01:16:01 PM

MICHAEL D BLUM
04/29/2021 01:22:43 PM

MICHAEL D NGUYEN
04/29/2021 02:16:10 PM

ROBERT BALL
04/29/2021 06:27:40 PM

Office of Prescription Drug Promotion

Internal Consult

****Pre-decisional Agency Information****

Please Note: The following review is for DRM only and should not be used to provide comments to the sponsor.

To: Kate Oswell, MA, Health Communications Analyst
Division of Risk Management (DRM)
Office of Surveillance and Epidemiology (OSE)

From: Rebecca Falter, PharmD, Regulatory Review Officer, OPDP

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP
Linda Wu, Safety Regulatory Project Manager, OSE
Naomi Boston, Team Leader, DRM
Brad Moriyama, Risk Management Analyst, DRM
Doris Auth, Associate Director, DRM
Jina Kwak, OPDP
Michael Wade, OPDP
CDER-OPDP-RPM

Date: April 13, 2021

Re: NDA 215014
EMPAVELI™ (pegcetacoplan) injection, for subcutaneous use
Comments on Draft Risk Evaluation and Mitigation Strategies (REMS) Materials

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Materials Reviewed

OPDP has reviewed the following proposed REMS materials for EMPAVELI (pegcetacoplan) injection, for subcutaneous use (Empaveli):

- Healthcare Provider (HCP) REMS Materials:
  - Empaveli Healthcare Provider Brochure
  - Empaveli Prescriber Enrollment Form
  - Empaveli Pharmacy Enrollment Form

- Direct-to-Consumer (Patient) REMS Materials:
  - Empaveli Patient Safety Guide
  - Empaveli Patient Wallet Card

- Empaveli REMS Website

The version of the draft REMS materials used in this review were sent from DRM (Kate Oswell) via email on March 30, 2021. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for Empaveli.

General Comment

Please remind Apellis Pharmaceuticals, Inc. that REMS materials are not appropriate for use in a promotional manner.

OPDP notes links such as www.BRANDREMS.com, toll-free numbers such as 1-8XX-BRAND (1-8XX-XXX-XXXX), and fax number such as 1-8XX-XXX-REMS. OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone. Furthermore, we remind Apellis Pharmaceuticals, Inc. that the REMS specific website should not be the sole source of approved REMS materials.

Comments are provided using the draft product labeling (PI) and Medication Guide (MG) for Empaveli dated March 26, 2021.

OPDP notes that the current Empaveli PI and MG are still being reviewed by DNH. Therefore, we recommend that the REMS materials be revised, as appropriate, to reflect all changes in the final approved label for Empaveli.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see "Specific Comments" below):

- Empaveli Healthcare Provider Brochure
- Empaveli Prescriber Enrollment Form
- Empaveli Pharmacy Enrollment Form
- Empaveli Patient Safety Guide
- Empaveli Patient Wallet Card
- Empaveli REMS Website

Specific Comments

OPDP considers the following statements promotional in tone and recommends revising them in the REMS pieces:

- Empaveli Healthcare Provider Brochure
- Empaveli Prescriber Enrollment Form
- Empaveli Patient Safety Guide
- Empaveli Patient Wallet Card
- Empaveli REMS Website
  - Throughout the Empaveli REMS materials there is reference to the "Patient Wallet Card."

    - **Risk**
      - In order to improve communication and avoid confusion for patients regarding the REMS materials for Empaveli, we recommend revising the title of this REMS material to "Patient Safety Card" to align with the language used in the draft Empaveli PI and MG.

- Empaveli Healthcare Provider Brochure
  - The cover page and page five of the Empaveli Healthcare Provider Brochure includes the following statement, (b) (4)

    - **Risk**
      - This claim may minimize REMS risk of the drug by failing to specifically refer to the Boxed Warning as part of the directive to the PI for more detailed safety information. For example, we note that the FDA-approved ULTOMIRIS® REMS Prescriber Safety Brochure states to, "Please see full Prescribing Information for ULTOMIRIS, including Boxed Warning regarding serious meningococcal infection for more detailed safety information" (emphasis added). We

recommend revising the Empaveli Healthcare Provider Brochure accordingly.

- Page two of the Empaveli Healthcare Provider Brochure includes the following statement under the header "**What is the BRAND REMS?**": (b) (4)

  - **Benefit**
    - This claim omits the following material information from the WARNINGS AND PRECAUTIONS, "Empaveli REMS" Section of the draft Empaveli PI (emphasis added):

      "Because of the risk of serious infections, EMPAVELI is available only through a restricted program under a REMS."

      By omitting this material information, this statement may suggest that Empaveli may be obtainable through mechanisms other than the REMS program, when this is not the case. We recommend revising the Empaveli Healthcare Provider Brochure to include this material information, consistent with the draft PI.

- Page two of the Empaveli Healthcare Provider Brochure includes the following statement under the header "**What is the BRAND REMS?**": (b) (4)

  - **Risk**
    - This claim minimizes REMS risks of the drug by omitting the following material information from the WARNINGS AND PRECAUTIONS, "Empaveli REMS" Section of the draft Empaveli PI (emphasis added):

      "Because of the risk of serious infections, EMPAVELI is available only through a restricted program under a REMS."

      By omitting this material information, the statement may minimize the severity of the REMS risk. We recommend revising the Empaveli Healthcare Provider Brochure to include the material information that the REMS program is to ensure prescribers are informed of the key risk of serious infections.

- Empaveli Pharmacy Enrollment Form
  - Page one of the Empaveli Pharmacy Enrollment Form includes the following statement under the header "**EMPAVELI™ REMS**": (b) (4) (b) (4)

    - **Benefit**
      - This claim omits the following material information from the WARNINGS AND PRECAUTIONS, "Empaveli REMS" Section of the draft Empaveli PI (emphasis added):

        "Because of the risk of serious infections, EMPAVELI is available only through a restricted program under a REMS."

        By omitting this material information, this statement may suggest that Empaveli may be obtainable through mechanisms other than the REMS program, when this is not the case. We recommend revising the Empaveli Pharmacy Enrollment Form to include this material information, consistent with the draft PI.

- Empaveli Patient Safety Guide
  - Page one of the Empaveli Patient Safety Guide includes the following statement under the header "**What are the serious risks of BRAND?**": "**Call your healthcare provider** or **get emergency care right away** if you have any of these signs and symptoms of a (b) (4) infection:"

    - Risk
      - This claim minimizes REMS risk of the drug by omitting the following material information from the "**What is the most important information I should know about EMPAVELI?**" Section of the draft Empaveli MG (emphasis added):

        "Call your healthcare provider or get emergency medical care right away if you get any of these signs and symptoms of a serious infection:"

        By omitting this material information, this statement may minimize the severity of the REMS risk. We recommend revising the Empaveli Patient Safety Guide to include this material information.

  - Page one and two of the Empaveli Patient Safety Guide includes the header "**Why are vaccines important?**" and the following statement under the header, (b) (4)

- Risk
  - This claim omits material information from the draft Empaveli MG necessary for the safe use of Empaveli. Specifically, the "**What is the most important information I should know about EMPAVELI?**" Section of the draft MG states (emphasis added):

    "If you have been vaccinated against these bacteria in the past, you might need additional vaccinations before starting EMPAVELI."

    We recommend revising this header and statement to include this material information from the draft Empaveli MG, in order to clarify that this statement refers to vaccinations against the bacteria specified by this REMS program, rather than any vaccine the patient may have had previously.

o Page two of the Empaveli Patient Safety Guide includes the following statement under the subheader "**Patient Wallet Card"**: "Carry this card at all times."

- Risk
  - This claim omits material information from the draft Empaveli MG necessary for the safe use of Empaveli. Specifically, the draft MG states (emphasis added):

    "Carry it with you at all times during treatment and for 2 months after your last EMPAVELI dose."

    We recommend revising this statement to include the material information from the draft Empaveli MG.

o Empaveli Patient Wallet Card
  o Page one of the Empaveli Patient Wallet Card includes the following statement, "**Call your healthcare provider** or **get emergency care right away** if you have any of these signs and symptoms of a (b) (4) infection:"

- Risk
  - This claim minimizes REMS risk of the drug by omitting the following material information from the "**What is the most important information I should know about EMPAVELI?**" Section of the draft Empaveli MG (emphasis added):

    "Call your healthcare provider or get emergency medical care right away if you get any of these signs and symptoms

of a serious infection:"

By omitting this material information, this statement may minimize the severity of the REMS risk. We recommend revising the Empaveli Patient Safety Guide to include this material information.

- Empaveli REMS Website
  - Page one of the Empaveli REMS Website includes the following statement under the header "**Patient Counseling"**: "Even if a patient stop *[sic]* using EMPAVELI, s/he should keep the EMPAVELI Patient Wallet Card with them for at least 2 months."

    - Risk
      - This claim omits material information from the draft Empaveli PI necessary for the safe use of Empaveli. Specifically, the PATIENT COUNSELING INFORMATION Section of the draft PI states (emphasis added):

        "Inform patients who discontinue EMPAVELI to keep the Patient Safety Card with them for 2 months after the last dose of EMPAVELI, …"

        We recommend revising this statement to include the material information from the draft Empaveli PI.

  - Pages two through five of the Empaveli REMS Website includes the following statement under the header "**EMPAVELI (pegcetacoplan) REMS Prescriber Enrollment Form"**: "EMPAVELI™ is only available through the EMPAVELI Risk Evaluation and Mitigation Strategy (REMS); (b) (4) (b) (4) "

    - **Risk**
      - This claim minimizes REMS risks of the drug by omitting the following material information from the WARNINGS AND PRECAUTIONS, "Empaveli REMS" Section of the draft Empaveli PI(emphasis added):

        "Because of the risk of serious infections, EMPAVELI is available only through a restricted program under a REMS."

        By omitting this material information, the statement may minimize the severity of the REMS risk. We recommend revising the Empaveli REMS Website to include the material information that the REMS program is to ensure prescribers

are informed of the key risk of serious infections.

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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CLINICAL INSPECTION SUMMARY

Date	March 10, 2021
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Julie Weisman, M.D., Medical Officer Tanya Wroblewski, M.D., Clinical Team Leader Ann Farrell, M.D., Division Director Carleveva Thompson, Regulatory Project Manager Division of Nonmalignant Hematology OCHEN
NDA	NDA 215014
Applicant	Apellis Pharmaceuticals, Inc.
Drug	Pegcetacoplan
NME	Yes
Division Classification	Complement cascade inhibitor & polyethylene glycol that binds to complement C3
Proposed Indication	Treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)
Consultation Request Date	September 25, 2020 (Priority Review)
Summary Goal Date	Before or on March 31, 2021
Action Goal Date	May 13, 2021
PDUFA Date	May 14, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from a single study, APL2-302, was submitted to the Agency in support of a New Drug Application (NDA 215014) for pegcetacoplan (APL-2), proposed for treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). A single clinical investigator site (Ilene Weitz, M.D.) and sponsor (Apellis Pharmaceuticals, Inc.) were inspected, in support of NDA 215014.

Based on these inspections, the study data derived from Dr. Ilene Weitz, the clinical investigator site and the sponsor t are considered reliable. The study data from Study APL2-302 submitted to the Agency appear acceptable in support of this NDA and the proposed indication.

II. BACKGROUND

Pegcetacoplan or APL-2 is a 40-kDa polyethylene glycol molecule which binds to complement C3 thereby inhibiting the complement cascade. The Sponsor proposes this drug indication for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH), with two previously approved therapies.

Four submitted studies to the FDA which will provide supportive information for the efficacy profile, Study APL2-CP-PNH-204, Study APL-2-202, Study APL-CP0514, and the ongoing study, APL-308. The efficacy results are based primarily on one Phase 3 controlled clinical trial (Study APL2-302), which forms part of the regulatory decision for approvability of this submitted NME application to the Agency.

Study APL2-302

Trial APL2-302 was a phase III, randomized, multicenter, open-label, active-comparator controlled study that enrolled 80 patients with PNH. The primary objectives of this study were to establish the efficacy and safety of pegcetacoplan (APL-2) compared with those of eculizumab in patients with paroxysmal nocturnal hemoglobinuria who continued to have Hb levels less than 10.5 g/dL despite treatment with eculizumab.

Protocol therapy consisted of either pegcetacoplan 1080 mg subcutaneously twice weekly or the current dosage of eculizumab, which continued as prescribed for 16 weeks. The study consisted of three parts: A four-week run-in period in which subjects treated with APL-2 and current dose of eculizumab concurrently, a 16-week randomized control period (RCP) in which subjects were randomized to pegcetacoplan or current eculizumab dosage, and an on-going 32-week open-label period in which all subjects are treated with APL-2. Responses were assessed by clinical and laboratory parameters.

The primary endpoint was change from baseline in hemoglobin levels through 16 weeks. Key secondary endpoints included transfusion avoidance and change from baseline to week 16 in absolute reticulocyte count, lactate dehydrogenase (LDH), and FACIT-Fatigue Scale score.

The primary efficacy population consisted of 80 patients with PNH and with hemoglobin less than 10 g/dL. The randomized patients consisted entirely of an adult population (age ~48.6 years).

Trial APL2-302 was conducted in 44 sites globally with 14 sites in the US. The date the first subject screened was on June 14, 2018 and the last date the last subject completed was on November 14, 2019.

The Division of Nonmalignant Hematology (DNH) requested inspection of a single clinical study clinical investigator site, a U.S. site with the highest number of reported protocol deviations. The review division also requested inspection of the sponsor’s site to assess clinical trial oversight adequacy.

III. RESULTS (by site)

1. **Ilene Weitz, M.D. / Site #01010**
   University of Southern California
   1441 Eastlake Avenue, Room 7310
   Los Angeles, California 90033

   Inspection dates: October 19 to 22, 2020

   A total of four study subjects were screened. Four study subjects were enrolled and received study treatment. All the enrolled study patients completed the study.

   The IRB for this study was the University of Southern California Institutional Review Board, at 1640 Marengo Street, Suite 700 Los Angeles, California.

   Records reviewed included but were not limited to: investigator agreements, financial disclosure forms, Institutional Review Board (IRB) approvals and documentation, delegation log, screening and enrollment log, monitoring log and monitoring reports, electronic case report forms (eCRFs), subject source records, test article control records, adverse event/serious adverse event documentation, and informed consent documentation.

   Source documents consisted of subject medical records/histories, vital statistics, laboratory reports, physical and neurological examination reports, physician reports, progress notes, notes to file and subject visit reports.

   Source records for all enrolled study patients at the site were reviewed and compared with the Applicant's submitted data listings for the site. The clinical study site retained study records. The primary efficacy endpoint data were verified against the data line listings. No discrepancies were noted. There was no under-reporting of serious adverse events.

   There were no objectionable conditions noted. For example, a review of this clinical study site's protocol deviations revealed no significant violations of the FDA regulations. No Form FDA-483, Inspectional Observations, issued.

2. **Apellis Pharmaceuticals, Inc.**
   100 5th Avenue, 3rd Floor
   Waltham, MA 02451

   Inspection dates: November 9 to 13, 2020

   An onsite inspection assessed Apellis Pharmaceuticals, Inc.'s responsibilities concerning its oversight of Study APL2-302.

The sponsor site audit involved review of organizational charts, standard operating procedures, investigator selection, monitoring plans, monitoring reports, transfer of responsibilities, correspondence, training records, FDA 1572's, financial disclosure forms, electronic case report forms (eCRFs), protocol deviations, protocol adherence, subject protection and ethical oversight, safety plans, adverse events reporting, data management, primary efficacy endpoint and investigational product accountability records.

Four clinical investigator sites underwent further regulatory documents review: (a) Gregory Ortega. M.D. (Site #01001, Orange County, FL), (b) Anita Hill, M.D. (Site #04001, Leeds, UK), (c) Jeffery Szer, M.D. (Site #02001, Melbourne, Australia), and (d) Carlos DeCastro, M.D. (Site #01009, Durham, NC).

The inspectional audit reviewed the site selection visit reports, Apellis emails to CROs with official site selection, "Site Selection Letters" and the Site Initiation Visit reports for Sites #01001, #04001, #02001, and #01009. Apellis followed their written SOPs and the Monitoring Plan. Site qualifications and availability of materials were documented within the site selection visit reports. No underreporting of serious adverse events was noted at these study sites.

In general, no regulatory deficiencies were observed during the inspection. There were no Form FDA-483, Inspectional Observations issued.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Min Lu, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 2, 2021

To: Carleveva Thompson, MS, Regulatory Project Manager, Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, Associate Director for Labeling, DNH

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for Empaveli® (pegcetacoplan) injection, for subcutaneous use

NDA: 215014

In response to DNH's consult request dated September 18, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Empaveli.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DNH (Carleveva Thompson) on February 16, 2021 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide and IFU were sent under separate cover on February 25, 2021.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 14, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 25, 2021
To:	Carleveva Thompson, MS Regulatory Project Manager **Division of Non-Malignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Robert Nguyen, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	EMPAVELI (pegcetacoplan)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 215014
Applicant:	Appellis

1 INTRODUCTION

On September 14, 2020, Apellis submitted for the Agency's review an original New Drug Application (NDA) 215014 for EMPAVELI (pegcetacoplan) injection, for subcutaneous use. Pegcetacoplan is a complement inhibitor developed for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Non-Malignant Hematology (DNH) on September 18, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for EMPAVELI (pegcetacoplan) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft EMPAVELI **(**pegcetacoplan) injection MG and IFU received on September 14, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 16, 2021.
- Draft EMPAVELI (pegcetacoplan) injection Prescribing Information (PI) received on September 14, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 16, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 12, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 215014
Product Name, Dosage Form, and Strength:	Empaveli (pegcetacoplan) injection 1,080 mg/20 mL (54 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Apellis Pharmaceuticals, Inc. (Apellis)
FDA Received Date:	September 14, 2020 and January 14, 2021
OSE RCM #:	2020-1939
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1. REASON FOR REVIEW

Apellis Pharmaceuticals, Inc. submitted NDA 215014 for Empaveli (pegcetacoplan) injection on September 14, 2020. Empaveli is a complement inhibitor proposed for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). We evaluated the proposed container label, carton labeling, Prescribing Information (PI), Medication Guide (MG), and Instructions for Use (IFU) for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND INFORMATION

Apellis is proposing the product to be supplied in a 20 mL vial. Each vial is intended to provide a single, fixed dose to be administered subcutaneously using a compatible, commercially available 510(k) cleared drug delivery system (e.g., infusion pump, syringe driver infusion system). On July 27, 2020 Apellis submitted a use-related risk analysis (URRA) and an Instructions for Use (IFU) labeling comparison to support that the results of a HF validation study are not needed to support the marketing application for the proposed product. Our review of the URRA concluded that Apellis did not need to submit the results of a human factors validation study for our review at that time.[a]

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP newsletters for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

[a] Little, C. Use Related Risk Analysis Review for pegcetacoplan. IND 123087. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 13. RCM No.: 2020-1580.

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, Prescribing Information (PI), Medication Guide (MG), and Instructions for Use (IFU) for Empaveli to identify deficiencies that may lead to medication errors and other areas of improvement.

Our review of the PI, IFU, container label, and carton labeling identified areas that can be modified to improve the clarity of the information presented. We find the MG acceptable from a medication error perspective at this time.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI, IFU, container label, and carton labeling can be improved to increase clarity of important information to promote the safe use of the product. We provide recommendations for the division in Section 4.1 and recommendations for Apellis in Section 4.2 below. We conclude the proposed Medication Guide (MG) is acceptable from a medication error perspective. We defer to Patient Labeling Team for recommendations for the MG.

4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information

A. General Comments
    1. Replace "TRADENAME" with the conditionally acceptable proprietary name "Empaveli" wherever it appears.

    1. As currently presented, the strength reads, "1080 mg/20 mL". We recommend stating numbers greater than or equal to 1,000 with a comma to prevent the reader from misinterpreting one-thousand "1000" as one-hundred "100" or ten-thousand "10000".[b]

B. Highlights of Prescribing Information
    1. Dosage Forms and Strengths
        a. We recommend including the recommended dose in the highlights section. For example, "Recommended dosage is 1,080 mg by subcutaneous infusion twice weekly via a commercially available pump (2.X)".
        b. We recommend revising the dosage form and strength statement to include the dosage form. Revise to "Injection: 1,080 mg/20 mL (54 mg/mL) in a single-dose vial".

[b] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015. Available from: https://www.ismp.org/tools/errorproneabbreviations.pdf

C. Dosage and Administration [2]

1. [redacted]
    a. We recommend deleting this section and incorporating pertinent information into the Administration section.

2. Dosage [redacted]
    a. We recommend revising this section to improve clarity and to use active voice. For example:

The recommended dose of EMPAVELI [redacted] is 1,080 mg by subcutaneous infusion twice weekly [redacted] via a commercially available [redacted] infusion pump that can deliver doses up to 20 mL.

Dosage for patients switching to [redacted] EMPAVELI from C5 inhibitors

- [redacted]
- After 4 weeks [redacted] discontinue [redacted] before continuing on monotherapy with [redacted] EMPAVELI.

Dose Adjustment

- For lactate dehydrogenase (LDH) level greater than 2 × the upper limit of normal (ULN), adjust tThe dosing regimen [redacted] to 1,080 mg every [redacted] three days [redacted]
- In the event of a dose increase, monitor LDH twice weekly for at least 4 weeks.

Missed Dose

- Administer EMPAVELI as soon as possible after a missed dose [redacted] Resume the regular dosing schedule [redacted] following the administration of the missed dose.

3. Administration [redacted]
    a. We recommend revising this section [redacted] and instead include concise, important administration information, as well as direct users to the separate Empaveli IFU and the infusion pump IFU for full administration instructions. For example:

2.3 [redacted] Administration

[redacted] **EMPAVELI is for subcutaneous infusion** using an infusion pump**.**

EMPAVELI is intended for use under the guidance of a healthcare provider. After proper training in subcutaneous infusion, a patient may self-administer, or the patient's caregiver may administer EMPAVELI, if a healthcare provider determines that it is appropriate.

[redacted]

- Refer to the EMPAVELI Instructions for Use and the infusion pump manufacturer's instructions for full preparation and administration information.
- Use aseptic technique when preparing and administering EMPAVELI.
- Prior to use, allow EMPAVELI to reach room temperature for approximately 30 minutes. Keep the vial in the carton until ready for use to protect from light.
- Visually inspect each vial of EMPAVELI for particulate matter or discoloration, whenever the solution and container permit. EMPAVELI is a clear, colorless to slightly yellowish solution. Do not use if the liquid looks cloudy, contains particles, or is dark yellow.
- Use a needleless transfer device (such as a vial adapter) or a transfer needle to fill the syringe.
- Rotate infusion sites (i.e. abdomen, thighs, hips, upper arms) from one infusion to the next. Do not infuse where the skin is tender, bruised, red, or hard. Avoid infusing into tattoos, scars, or stretch marks.
- If multiple infusion sites are needed, ensure they are at least 3 inches apart.
- The typical infusion time is approximately 30 minutes (if using two infusion sites) or approximately 60 minutes (if using one infusion site).
- Discard any unused portion.

D. Dosage Forms and Strengths [3]

1. We recommend revising this statement to read "Injection: 1,080 mg/20 mL (54 mg/mL) clear, colorless to slightly yellowish solution in a single-dose vial".

E. How Supplied/Storage and Handling [16]

1. We recommend revising the 1st statement to include the correct dosage form by replacing (b) (4) with "injection".

2. We recommend revising the 2nd statement to include the proposed NDC for the outermost carton and to improve the description of the product packaging. For example, "Empaveli is available in 20 mL single-dose vials individually packaged in cartons that are supplied in an 8-count convenience carton. NDC XXXXXX-XXX-XX".

Instructions for Use

A. General Comments
    1. Replace “TRADENAME” with the conditionally acceptable proprietary name “Empaveli” wherever it appears.

B. [redacted] (b) (4)
    1. We recommend revising the first paragraph to increase the clarity of the information presented. For example, revise to read:

[redacted] (b) (4)

C. Step 3
    1. We recommend revising the text in sub-step B to improve clarity. Revise to read “Pull back the plunger to the 20 mL mark to fill the syringe with air”.

    2. We recommend revising sub-step I to instruct users to recap the transfer needle before unscrewing the needle from the syringe to prevent needlestick injuries. We also recommend including corresponding figures to demonstrate the action of recapping the needle, pushing the needle cap on, and twisting off the needle. For example, revise to read “To remove the transfer needle, use one hand to slide the needle into the needle cap and scoop upwards to cover the needle. Once the needle is covered, push the needle cap towards the syringe to fully attach it with one hand to prevent an accidental stick with the needle. Twist off and remove the transfer needle (see Figure X).”

4.2 RECOMMENDATIONS FOR APELLIS PHARMACEUTICALS INC.

A. General Comments for All Labels and Labeling

1. Replace "TRADENAME" with the conditionally acceptable proprietary name "Empaveli.

2. As currently presented, the strength reads, "1080 mg/20 mL". We recommend stating numbers greater than or equal to 1,000 with a comma to prevent the reader from misinterpreting one-thousand "1000" as one-hundred "100" or ten-thousand "10000".[c]

2. We recommend revising (b) (4) to read "For Subcutaneous Infusion Only" to ensure this information is not overlooked. The "Solution for subcutaneous infusion" statement may be removed from the side panel.

3. We recommend un-bolding and decreasing the font size of the "Rx Only" statement so that it does not compete in prominence with other critical information on the principal display panel (PDP).

B. Container Label

1. As currently presented, the manufacturer name on the PDP competes in prominence with other critical information. We recommend removing "Apellis Pharmaceuticals Inc." from the PDP as the manufacturer information is stated on the side panel.

2. We recommend revising the "Single-dose vial" statement to read "Single-Dose Vial. Discard unused portion."

3. To ensure consistency with the Prescribing Information, we recommend adding a Dosage statement which reads "Dosage: see prescribing information".

C. Carton Labeling

1. As currently presented, the Medication Guide statement is located on a side panel. Per 21 CFR 208.24(d), the label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner. As such, we recommend stating "Dispense the enclosed Medication Guide to each patient" prominently, as space will allow, on the PDP in accordance with 21 CFR 208.24(d).

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[c] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015. Available from: https://www.ismp.org/tools/errorproneabbreviations.pdf

2. To ensure none of the storage information is overlooked, we recommend combining the two storage statements to read "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light".

3. To ensure consistency with the Prescribing Information, we recommend revising the Dosage and Administration statement to read "Dosage: see prescribing information" and deleting the (b) (4) statement.

4. On the single-count carton, we recommend revising the (b) (4) statement to read "1 Single-Dose Vial. Discard unused portion."

5. On the 8-count carton, we recommend adding "Discard unused portion" on the line below the "8 Single-Dose Vials" statement.

6. As currently presented, the human-readable portion of the product identifier on the 8-count carton does not include an NDC or GTIN. If the GTIN is included as part of the human-readable portion, we recommend including the NDC somewhere else on the carton. See *Draft Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (September 2018).*[d]

[d] When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents

APPENDICES: METHODS & RESULTS FOR MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Empaveli received on September 14, 2020 from Apellis Pharmaceuticals, Inc.

Table 2. Relevant Product Information for Empaveli	
Initial Approval Date	N/A
Active Ingredient	(pegcetacoplan)
Indication	For the treatment of paroxysmal nocturnal hemoglobinuria (PNH)
Route of Administration	subcutaneous infusion
Dosage Form	injection (solution)
Strength	1,080 mg/20 mL (54 mg/mL)
Dose and Frequency	1,080 mg subcutaneous infusion twice weekly
How Supplied	20 mL single-dose vial
Storage	Store refrigerated at 2°C to 8°C protected from light

APPENDIX B. PREVIOUS DMEPA REVIEWS and SPONSOR/AGENCY INTERACTIONS

On January 25, 2021, we searched for previous DMEPA reviews and sponsor/agency interactions relevant to this current review using the terms, "pegcetacoplan" and "IND 123087". Our search identified one previous review and one previous sponsor/agency interaction, and we confirmed that our previous recommendations were implemented. See Tables 3 and 4 below.

Table 3. Summary of Previous DMEPA Reviews for Empaveli

Reviewer	Document Title	Application	Date	RCM No.	Conclusion
Little, C.	Use-Related Risk Analysis Review for Pegcetacoplan	IND 123087	2020 OCT 13	2020-1580	Based on our review of your use-related risk analysis (URRA) and justification, at this time, we determined that the results of a human factors validation study do not need to be submitted for Agency review to support your marketing application.

Table 4. Summary of Previous Sponsor/Agency Interactions

Interaction Type	Date	Summary
Type B Meeting	2020 MAY 20	*See RCM 2020-711* Summary of DMEPA Additional Comments: Based on information presented in your meeting package, we note that your proposed product is intended to be delivered as a subcutaneous infusion via an infusion pump. We recommend you conduct a proactive risk assessment if you have not already completed one. The proactive risk assessment should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures. If models of the same or similar products exist, your proactive risk assessment should incorporate applicable information on known use-related problems with those products. Useful information can be obtained from your own experience as well as from public sources such as literature, adverse event reports, and product safety communications. Based on the aforementioned information and data, you should determine whether you need to submit the results of a human factors

		(HF) validation study conducted under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product. If you determine that an HF validation study does not need to be submitted for your product, submit your risk analysis and justification for not submitting the HF validation study to the Agency for review under the IND. The Agency will notify you if we concur with your determination.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of Failure Mode and Effects Analysis,[e] along with post-market medication error data, we reviewed the following labels and labeling submitted by Apellis Pharmaceuticals, Inc.:

- Container Label received on September 14, 2020
- Carton Labeling received on September 14, 2020
- Prescribing Information (no image shown) received on January 14, 2021
  \\CDSESUB1\evsprod\nda215014\0022\m1\us\draft-uspi-tracked.doc
- Medication Guide (no image shown) received on January 14, 2021
  \\CDSESUB1\evsprod\nda215014\0022\m1\us\draft-medguide-tracked.docx
- Instructions for Use (no image shown) received on January 14, 2021
  \\CDSESUB1\evsprod\nda215014\0022\m1\us\draft-ifu-tracked.docx

G.2 Labels and Labeling

Container Label

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

STEPHANIE L DEGRAW
02/12/2021 10:51:51 AM

HINA S MEHTA
02/12/2021 05:44:04 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA-215014
Submission Number	001
Submission Date	9/14/2020
Date Consult Received	9/22/2020
Drug Name	Pegcetacoplan (APL-2)
Indication	Paroxysmal nocturnal hemoglobinuria
Therapeutic dose	1080 mg twice weekly (as SC infusion)
Clinical Division	DNH

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 9/22/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND-123087 dated 02/14/2017 in DARRTS (link);
- Previous IRT review under IND-123087 dated 06/28/2017 in DARRTS (link);
- Previous IRT review under IND-123087 dated 01/09/2020 in DARRTS (link);
- Sponsor's clinical study protocol # APL2-101 (SN0001; link);
- Sponsor's clinical study report # APL2-101 (SN0001; link);
- Sponsor's clinical study protocol # APL2-302 (SN0001; link);
- Sponsor's clinical study protocol # APL2-302 (SN0001; link);
- Sponsor's cardiac safety assessment report # APL2-EX20-CP-004 (SN0001; link);
- Investigator's brochure Ed.8.0 (SDN001; link);
- Sponsor's proposed product label (SN0001; link);
- Highlights of clinical pharmacology and cardiac safety (SN0001; link).

1 SUMMARY

No large mean increase in the QTc interval (i.e., >20 msec) was observed in this QT assessment of pegcetacoplan. However, we are reluctant to draw conclusions of lack of an effect in an absence of a positive control, large exposure margin, or an integrated nonclinical safety assessment conduct according to best practices (ICH S7b Q&A 1.1 and 1.2).

The effect of pegcetacoplan was evaluated using data from 2 clinical studies (Studies # APL2-101 and APL2-302). Study # APL2-101 was a phase-1, double-blind, randomized study of daily, twice-weekly and once-weekly pegcetacoplan in healthy subjects. Study # APL2-302 was a phase-3, randomized, multi-center, open-label, active-comparator, controlled study evaluating the efficacy and safety of pegcetacoplan in patients with paroxysmal nocturnal hemoglobinuria. Both studies included doses to cover therapeutic

exposures at steady-state. There are no known clinical scenarios resulting in increased exposures of pegcetacoplan (see Section 3.1).

The data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that pegcetacoplan is associated with large mean increases in the QTc interval (refer to Section 4.5) – see Table 1 for overall results.

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

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

For further details on the FDA analysis, please see Section 4.

The findings of this analysis are further supported by the available nonclinical data (Sections 3.1.2) and by time analysis (Section 4.3) and categorical analysis (Section 4.4).

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SN0001 (link) from the IRT. Our changes are highlighted (*addition*, ~~*deletion*~~). Each Section is followed by a rationale for the changes made. Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

At the recommended dose of <Tradename>, no large mean increases (i.e., 20 msec) in QTc interval was observed.

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Apellis Pharmaceuticals, Inc. is developing pegcetacoplan (APL-2; 43.5 kDa - two 1899.9 Da peptides linked to nominal 40 kDa bifunctional PEG) for the management of paroxysmal nocturnal hemoglobinuria (PNH) (b) (4) (b) (4) Pegcetacoplan (APL-2) is a PEGylated peptide with identical small pharmacologically active cyclic pentadecapeptides (MW: 1899.9) which binds to complement proteins (mainly C3) and exert a broad inhibition of the complement cascade. (b) (4)

The product is formulated as sterile solution (1080 mg in 20 mL; 54 mg/mL; single-dose vial) for subcutaneous infusion (using a syringe system infusion pump). The proposed therapeutic dose for patients with PNH is 1080 mg twice weekly (as subcutaneous infusion) which was evaluated in the Phase 3 studies (Studies # APL2-302 and APL2-308). This dosing regimen is expected to provide similar exposure of APL-2 at steady state to that from an earlier dosing regimen of 270 mg/day (as subcutaneous injection). The peak concentrations of 650 µg/mL (Tmax: 108 to 144 h; half-life: ~230 h) are expected at steady-state with therapeutic doses. Sponsor states that pegcetacoplan undergo proteolytic degradation without significant metabolism by the CYP450 enzymes and highlights that it has a low drug interaction potential as a victim drug. Further, the sponsor also highlights that age, sex, race, renal, or hepatic function has no impact on the pharmacokinetics of pegcetacoplan.

Previously, the IRT reviewed the sponsor's thorough QT study substitution requested and accepted to exclude large mean QTc effects (i.e., 20 msec), for this indication as it is not possible to study APL-2 in healthy subjects (Dt: 02/14/2017). Subsequently, the sponsor submitted phase-3 study protocol (APL2-301: randomized, multi-center, double-blind, placebo-controlled trial to evaluate the efficacy and safety of APL-2 in patients with paroxysmal nocturnal hemoglobinuria who require RBC transfusions despite receiving therapy with eculizumab) which was found to be reasonable to exclude large mean changes in the QTc interval. However, it was recommended that consider using only the data from the double-blind placebo-controlled period for the primary analysis of this study. Additionally, the QT-IRT was concerned that the exclusion criteria in Section 4.4.4 in the QT evaluation and statistical analysis plan for the by-time or categorical analysis may result in too few patients for analysis.

Recently, the sponsor planned to evaluate the effect of APL-2 on ECG parameters in the Phase 3 clinical study (Study # APL2-302) and Phase 1 clinical study (Study # APL2-101). The IRT review indicated that the sponsor's proposal was reasonable to exclude large mean

changes in the QTc intervals (i.e., 20 msec) and the IRT provided general comments on data modeling and submission. Refer to the previous IRT reviews dated 01/09/2020 in DARRTS (link).

Study # APL2-101 was a phase-1, double-blind, randomized study of daily, twice-weekly and once-weekly pegcetacoplan in healthy subjects. Although this study utilized placebo, the data were analyzed by the IRT as the change from baseline considering that there were limited number of subjects in placebo group (total, n=4; C1, n=1; C2, n=1; C3, n=2) and other cohorts (C4 & C5; open-label) did not include subjects on placebo. Study # APL2-302 was a phase-3, randomized, multi-center, open-label, active-comparator, controlled study evaluating the efficacy and safety of pegcetacoplan in patients with paroxysmal nocturnal hemoglobinuria.

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's highlights of clinical pharmacology and clinical safety.

An in vitro hERG assay (Study 13ZTX-001) evaluating pegcetacoplan and PEG40 found that neither agent had an effect on myocardial repolarization.

An in vivo study (Study 13CATX-005) in telemeterized cynomolgus monkeys given single SC doses of pegcetacoplan or PEG40 found no effect on clinical, body temperature, cardiovascular or respiratory parameters.

Reviewer's assessment: *The sponsor evaluated the effects of pegcetacoplan (APL-2) and PEG40 on hERG current, a surrogate for IKr that mediate membrane potential repolarization in cardiac myocytes. The GLP hERG study report (link) describes the potential effects of pegcetacoplan on the hERG current in HEK293 cells. The hERG current was assessed at physiological temperature (37 ± 1 ^{o}C), using a step-step voltage protocol consisting of a depolarizing step from -75 mV to +10 mV (0.5 s), followed by a repolarizing step to -40 mV (0.5 s). The voltage waveform was repeated every 10 seconds. The sponsor's voltage protocol is different from the recommended hERG current protocol by the FDA (link). The reviewer does not expect protocol differences to impact hERG current pharmacology. The positive control (0.1 µM E-4031) inhibited hERG potassium current by 86.9%. This result confirms the sensitivity of the test system to hERG inhibition. Samples of the test article formulation solutions collected from the tip of the perfusion line were analyzed for concentration verification. The results from the sample analysis indicated that the measured concentrations of pegcetacoplan at all test concentrations were within ± 5.0% of nominal concentrations, thereby meeting the acceptance criteria and nominal concentrations were used to describe drug effects.*

The sponsor concluded that pegcetacoplan and PEG40 were associated with little or no reduction in hERG current amplitude over a concentration range of 1 µM to 300 µM. The IC50 values for pegcetacoplan and PEG40 to inhibit the hERG current are expected to be greater than 300 µM.

The sponsor submitted raw data (link) of hERG assay on October 15, 2020. However, hERG current recordings from these raw data showed that there was only one current trace in control solution and one current trace in each tested drug solution in most of cells. The recording quality (current stability) of the data cannot be assessed with the limited data provided by the sponsor. In addition, the voltage protocol (from -75 mV to 10 mV for

2 s, followed by a 1 s repolarizing pulse to -40 mV) in the submitted raw data is different from the one in the study report. Moreover, most hERG recordings showed small current level with high noise level (100-200 pA noise).

The in vivo cardiovascular pharmacology study (link) assessed effects of subcutaneous administrations (APL-2) of pegcetacoplan on ECG parameters and cardiovascular hemodynamic in 8 telemetered monkeys. All animals were dosed with control article (PEG40) on Day 1. On Day 15, the Group 1 animals received APL-2 at 28 mg/kg/day while the Group 2 animals received APL-2 at 140 mg/kg/day. The mean Cmax at Day 23 were 625 µg/mL in high dose group (140 mg/kg/day) which was lower than that in the supra-therapeutic exposure level in humans (SC at 1080 mg twice a week and the projected steady-state plasma concentration was 706 µg/mL in human). There were no positive control drugs in the study. All of the observed QTca intervals were within the normal range for the study animals at two dose levels.

In summary, the in vitro hERG assay didn't meet the best practices for the in vitro assay according to the new ICH S7B Q&A 2.1 (link) due to limited raw data to demonstrate hERG current stability, poor data quality and inconsistent voltage protocol used in the study. The in vivo assay didn't meet the new ICH S7B Q&A 2.1 due to lack of positive drugs and slight less than human supra exposure in the study. Therefore, both in vitro and in vivo assays cannot be included in an integrated risk assessment.

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

The primary analysis for APL-2 was based on exposure-response analysis, please see Section 3.2.3 for additional details. Sponsor provided descriptive statistics for both studies for all intervals (QT, HR, PR and QRS).

Reviewer's comment: *FDA reviewer's analysis results are similar to sponsor's analysis results. Please see Section 4.3 for details.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTcF (i.e., > 500 msec or > 60 msec over baseline, PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *FDA reviewer's analysis results are similar to the sponsor's analysis results for QTcF, PR and QRS. Four subjects experienced HR greater than 100 beats/min in study APL-302. Please see section 4.4 for details.*

3.2.3 Exposure-Response Analysis

The sponsor explored the PK/PD relationship between the change from baseline in QTc interval (ΔQTcF) and the serum concentration of pegcetacoplan using linear mixed mixed-effects model using pooled data from studies # APL2-302 and APL2-101, as well as separately for each study.

The sponsor's analysis (using Study # 302) shows that there was a slight positive slope of 0.0072 ± 0.0108 msec/µg/mL (p-value 0.5151; not statistically significant) for the relationship between ΔQTcF and serum concentration of pegcetacoplan. Based on the linear model the predicted ΔQTcF was 1.42 msec (upper 90% CI 2.95 msec) at the mean Cmax of 720 µg/mL. Similarly, the sponsor's analysis (using Study # 101) shows that there was a slight negative slope of -0.0074 ± 0.0052 msec/µg/mL (p-value 0.1672; not statistically significant) for the relationship between ΔQTcF and serum concentration of pegcetacoplan. Based on the linear model the predicted ΔQTcF was -1.29 msec (upper 90% CI 2.30 msec, bootstrap) at the mean Cmax of 650 µg/mL. The Sponsor's analysis indicates an absence of significant QTc prolongation upon SC administration of pegcetacoplan.

Reviewer's comment: The conclusion of the reviewer's analysis agreed with the sponsor's analysis. Please see Section 4.5 for additional details.

3.2.4 Safety Analysis

3.2.4.1 Study # APL2-101 (SN0001; link);

There were no deaths and no SAEs in this study.

Upper respiratory tract infection events in 3 subjects were deemed by the investigator to be possibly related to study drug.

Two subjects (pooled placebo group and Cohort 5, SN) had increased ALT and increased transaminases (ALT and AST). These events were considered by the investigator to be possibly related to study drug.

Nearly all subjects who were administered study drug (39 of 40) had an ISR. Injection site erythema was the most common report, followed by injection site induration, pain, swelling, and pruritus. Subjects in Cohort 3 (pegcetacoplan 2600 mg once weekly) reported the fewest of ISR.

3.2.4.2 Study # APL2-302 (SN0001; link);

Run-in period: There was one SAE of sepsis, which was considered related to both eculizumab and pegcetacoplan, but the SAE resolved despite continued dosing of both drugs. There were no discontinuations due to TEAEs during the run-in period.

Randomized controlled period: Thirty-six subjects in the pegcetacoplan group (87.8%) and 34 subjects (87.2%) in the eculizumab group reported at least 1 TEAE. The numbers and proportions of subjects with SAEs, as well as those of treatment-related SAEs, were similar in the pegcetacoplan and eculizumab groups.

Seven subjects in the pegcetacoplan group had 8 SAEs (7 unique events), and 6 subjects in the eculizumab group had 11 SAEs. One subject in each treatment group had an SAE that was considered related to treatment. There were more TEAEs in the pegcetacoplan group

than the eculizumab group, which is attributable to the greater frequency of injection site reactions (ISRs) in the pegcetacoplan group. None of the ISRs were severe, serious, or led to study drug discontinuation.

Three subjects in the pegcetacoplan group discontinued because of TEAEs of breakthrough hemolysis. These discontinuations (7.3% in the pegcetacoplan group and 0 in the eculizumab arm) relate to subjects who reverted to the currently approved treatment for PNH (eculizumab). Overall, TEAEs of hemolysis occurred less frequently in the pegcetacoplan group than in the eculizumab group (9.8% vs 28.2%, respectively).

Reviewer's comment: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in these studies.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 beats/min) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Digitized ECGs from Study # 101 were uploaded, but analysis quality can't be determined, automatic measurements were used in the analyses. Waveforms from Study # 302 were reviewed. Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY TIME ANALYSIS

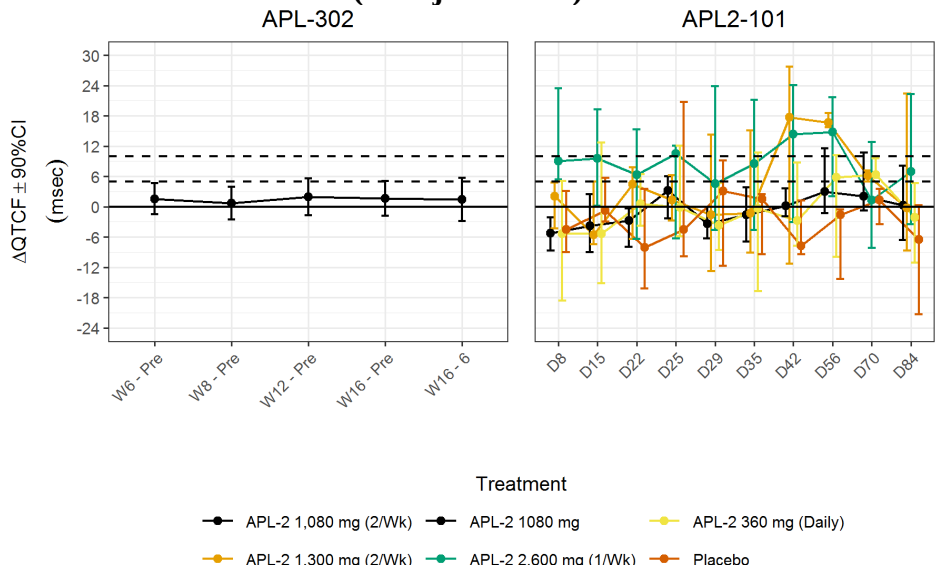
The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG.

FDA reviewer reviewed two studies: APL-302 and APL2-101. In study APL-302, data from week 6 to week 16 were used for by-time analysis. There were 41 subjects in APL-2 treatment arm (APL-2 1080 mg). We pooled doses in study APL2-101. There were 24 subjects in APL-2 1,080 mg (2/wk) treatment arm, 4 subjects in each of the other treatment arms. The statistical reviewer evaluated the ΔQTcF, ΔHR, ΔPR and ΔQRS effects using descriptive statistics: mean and 90% CI for study APL-302, median and 90% CI for study APL2-101.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for different treatment groups.

Figure 1: Mean (APL-302), Median (APL2-101) and 90% CI of ΔQTcF Timecourse (unadjusted CIs).



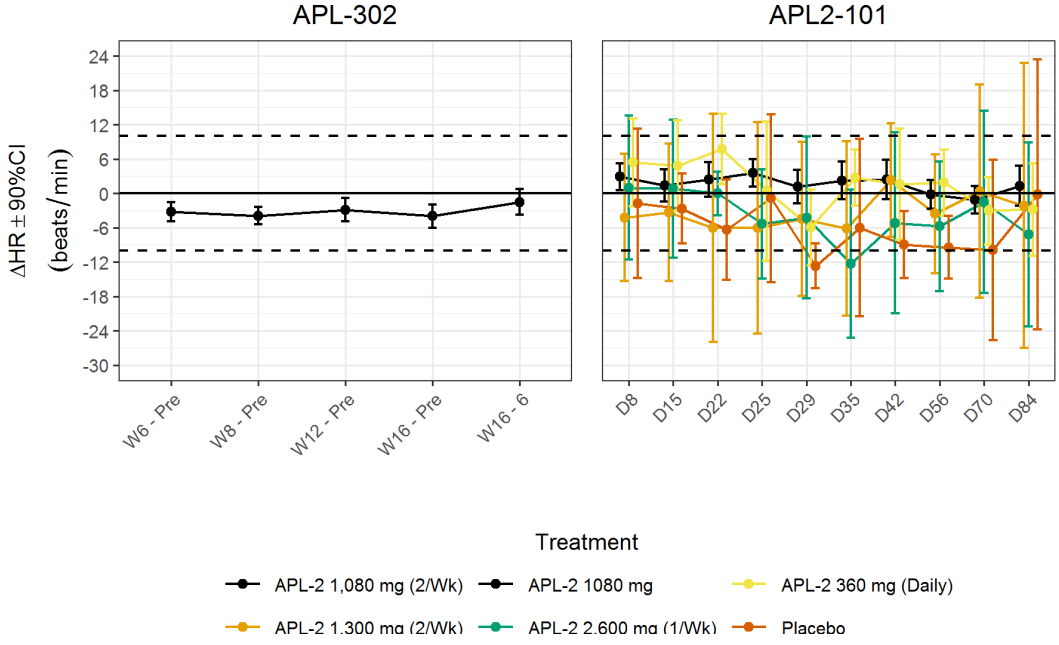
4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔHR for different treatment groups.

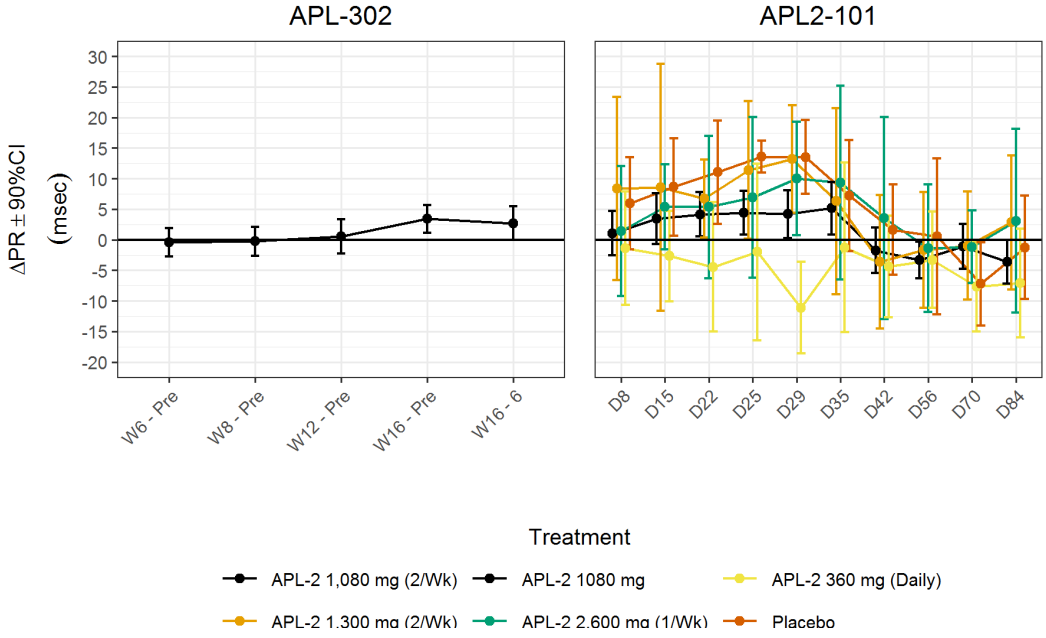
Figure 2: Mean (APL-302), Median (APL2-101) and 90% CI of ΔHR Timecourse



4.3.3 PR

Figure 3 displays the time profile of ΔPR for different treatment groups.

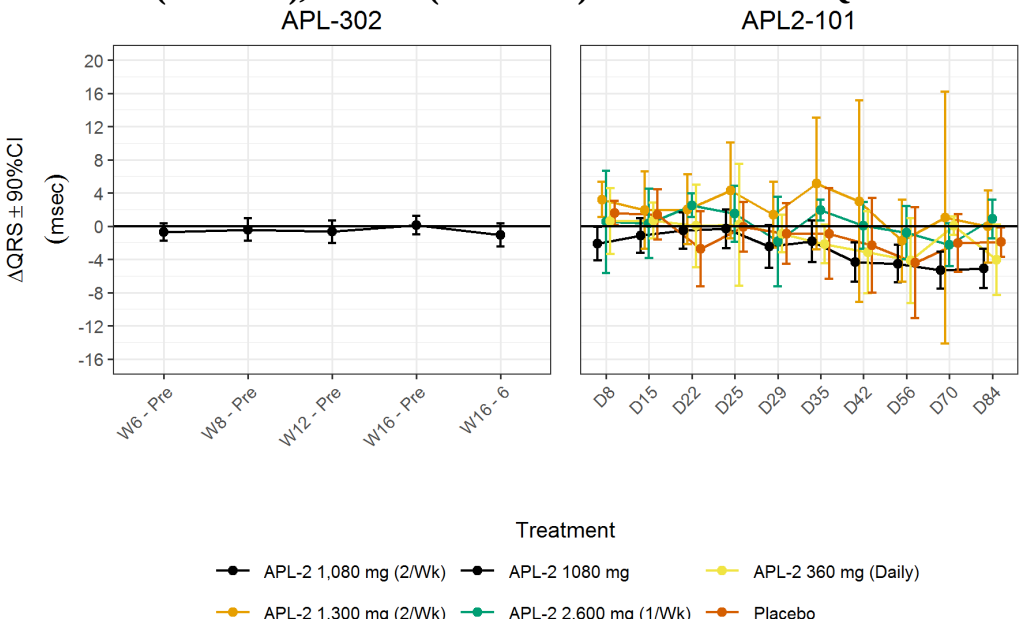
Figure 3: Mean (APL-302), Median (APL2-101) and 90% CI of ΔPR Timecourse



4.3.4 QRS

Figure 4 displays the time profile of ΔQRS for different treatment groups.

Figure 4: Mean (APL-302), Median (APL2-101) and 90% CI of ΔQRS Timecourse



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs in both studies (APL-302 and APL2-101).

4.4.1 QTc

None of the subjects in both studies experienced QTcF greater than 500 msec or ΔQTcF in any dose levels APL-2.

4.4.2 HR

Table 2 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). There were two subjects in APL-2 1080 mg and Eculizumab group and 2 subjects in randomized part of eculizumab monotherapy experienced HR >100 beats/min in study APL-302.

Table 2: Categorical Analysis for HR (maximum)

Study Identifier	Treatment	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
APL-302	APL-2 1080 mg	41	346	41 (100.0%)	346 (100.0%)	0 (0%)	0 (0%)
APL-302	APL-2 1080 mg and Eculizumab	79	321	77 (97.5%)	319 (99.4%)	2 (2.5%)	2 (0.6%)
APL-302	Randomized part of APL2-1080 mg monotherapy	39	259	39 (100.0%)	259 (100.0%)	0 (0%)	0 (0%)
APL-302	Randomized part of Eculizumab monotherapy	37	248	35 (94.6%)	245 (98.8%)	2 (5.4%)	3 (1.2%)

4.4.3 PR

None of the subjects experienced PR above 220 msec with 25% increase over baseline in different dose levels of APL-2.

4.4.4 QRS

None of the subjects experienced QRS above 120 msec with 25% increase over baseline in different dose levels of APL-2.

4.5 EXPOSURE-RESPONSE ANALYSIS

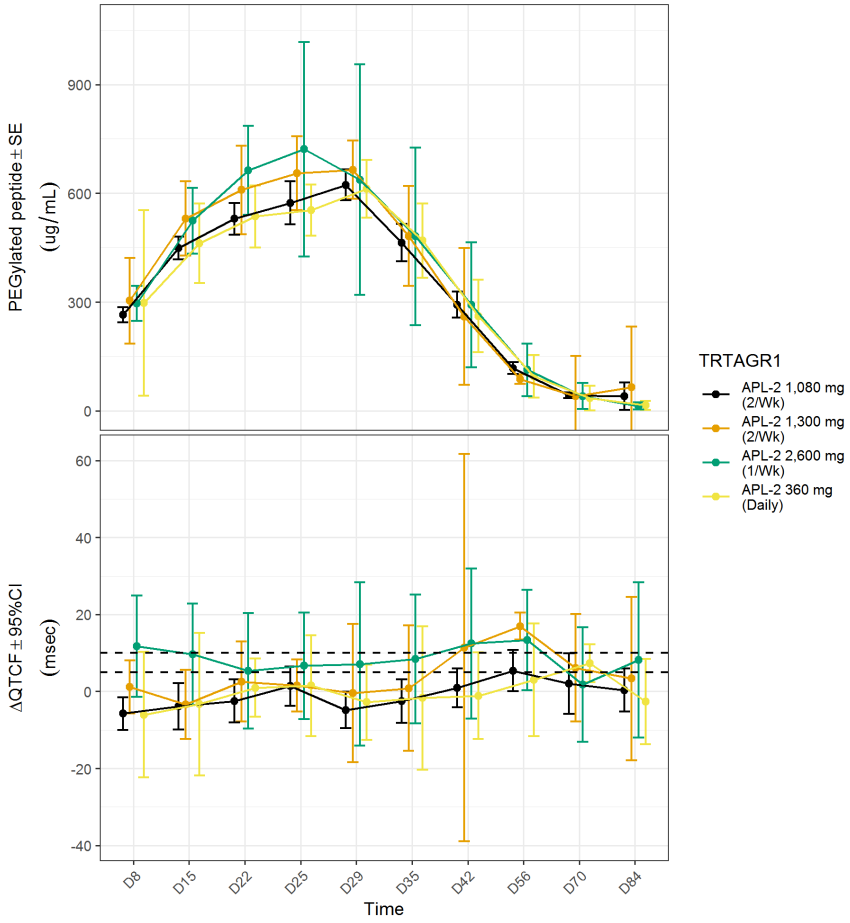
The objective of the clinical pharmacology analysis was to assess the relationship between serum concentration of pegcetacoplan and ΔQTcF. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

Prior to evaluating the relationship between pegcetacoplan concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between pegcetacoplan concentration and ΔQTc and 3) presence of non-linear relationship.

Figure 2 shows the time-course of ΔHR, which shows an absence of significant ΔHR changes. There were limited subjects in Study # ALP2-101 for dose groups 360, 1300, and

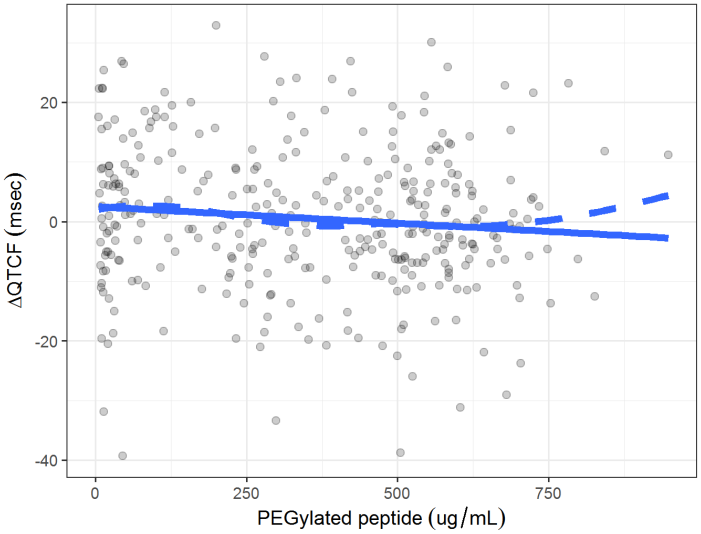
2600 mg. Figure 5 evaluates the time-course of pegcetacoplan concentration and ΔQTc and do not appear to show significant hysteresis.

Figure 5: Time course of pegcetacoplan concentration (top) and QTc (bottom)



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between pegcetacoplan concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between pegcetacoplan concentration and ΔQTcF and supports the use of a linear model.

Figure 6: Assessment of linearity of concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provide in Table 3.

Figure 7: Goodness-of-fit plot for QTc

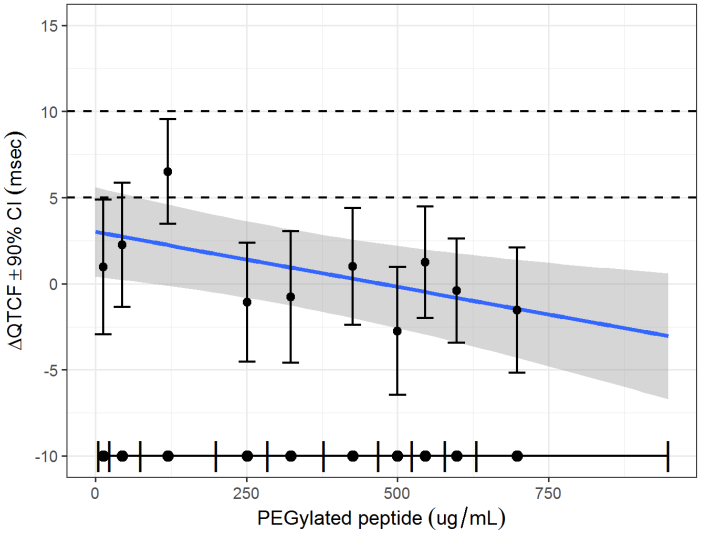


Table 3: Predictions from concentration-QTc model

TRTAGR1	PEGylated peptide (µg/mL)	ΔQTCF (msec)	90.0% CI (msec)
APL-2 1,080 mg (2/Wk)	594.6	-0.8	(-3.4 to 1.8)
APL-2 360 mg (Daily)	610.3	-0.9	(-3.5 to 1.7)
APL-2 1,300 mg (2/Wk)	665.9	-1.2	(-4.0 to 1.5)
APL-2 2,600 mg (1/Wk)	740.0	-1.7	(-4.7 to 1.2)

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