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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	21-7171
Supporting document/s:	SDN001
Applicant's letter date:	5/26/2022
CDER stamp date:	5/26/2022
Product:	Syfovre® (pegcetacoplan)
Indication:	For the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)
Applicant:	Apellis Pharmaceuticals Inc (Waltham, MA)
Review Division:	Division of Ophthalmology Products
Reviewer:	Erin Ruhland, PhD
Supervisor/Team Leader:	Lori Kotch, PhD, DABT
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1 Executive Summary

1.1 Introduction

- Apellis Pharmaceuticals, Inc. proposes Syfovre® for geographic atrophy (GA) secondary to age-related macular degeneration (AMD).
- Syfovre® (also known as APL-2 or pegcetacoplan) is composed of two small cyclic peptides covalently coupled via a linker to each end of a linear 40kDa polyethylene glycol (PEG40) chain. The peptide portion of the drug (APL-1/POT-4/AL-78898A; compstatin derivative) is a small 13-amino cyclic peptide with 12 natural amino acids and a single synthetic amino acid (methlyltryptophan).
- APL-1 binds to complement C3 and is a broad inhibitor of the complement cascade. The pegylation of the molecule imparts slower elimination from mammalian systems following administration.
- The nonclinical studies conducted by the Applicant support the approval the NDA.

1.2 Brief Discussion of Nonclinical Findings

- APL-2 is only pharmacologically relevant in monkeys and humans due to the species specificity of compstatin (the active moiety in APL-2) and its inhibitory effect on complement C3. Although only monkeys were used in ocular toxicity studies, both rabbits and monkeys were used in repeat-dose systemic toxicology studies.
- In systemic toxicity studies, subcutaneous administration of APL-2 in rabbits and monkeys resulted in findings of histiocytic infiltrates and macrophage vacuolation in several tissues, most notably the renal tubules and brain choroid plexus. It is thought that these effects are mediated by the PEG moiety in APL-2 since similar findings were reported in a PEG control group. In the monkey, minimal renal tubular degeneration was observed at the high dose.
- Intravitreal injection of APL-2 in monkeys resulted in low systemic exposure and no adverse ocular or systemic toxicity.
- The Applicant markets a systemic formulation of pegcetacoplan at a much higher systemic dose of pegcetacoplan (Empaveli®). Empaveli® is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).Nonclinical sections of the labeling for Syfovre® are based on the same studies conducted for the approval of Empaveli®.

1.3.1 Approvability

- The NDA is approvable from nonclinical pharmacology/toxicology standpoint.

1.3.3 Applicant's Proposed Labeling (Sections 8, 12.1 and 13 only)

8 USE IN SPECIFIC POPULATIONS

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

2 Drug Information

2.1 Drug

CAS Registry Number: 2019171-69-6

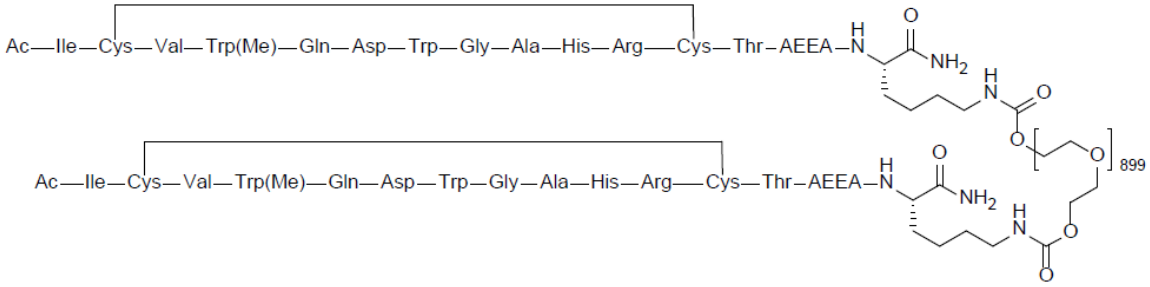
Generic Name: Pegcetacoplan

Code Name: APL-2, Syfovre®

Chemical Name: Poly(oxy-1,2-ethanediyl), α-hydro, ω-hydroxy-, 15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-α-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2→12)-(disulfide)

Molecular Formula/Molecular Weight: $C_{1970}H_{3848}N_{50}O_{947}S_4$ / 43.5 kDa

Structure or Biochemical Description:



Pharmacologic Class: Complement inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 124,784; initial IND for Syfovre and current NDA/indication
- NDA 215014; approved 5/14/2021 for same Applicant (and referenced as a relevant NDA on Form 356h). Empaveli® (pegcetacoplan) is approved for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). The recommended dose of EMPAVELI is 1,080 mg by subcutaneous infusion twice weekly.

2.3 Drug Formulation

Pegcetacoplan, solution for intravitreal injection, 15 mg/0.1 mL is a sterile, aqueous, (b) (4) solution for intravitreal administration. Each single-use vial contains (b) (4) of pegcetacoplan in (b) (4) solution. Each vial delivers a single dose of 0.1 mL solution containing 15 mg of pegcetacoplan.

Ingredient	Quality Standard	Function	Quantity per mL	Quantity per vial[a]
Pegcetacoplan	In-house standard	Drug Substance	150.0 mg[b]	15.0 mg[b]
Trehalose dihydrate	NF/Ph.Eur./JP	(b) (4)	59.5 mg	5.95 mg
Glacial acetic acid	USP/Ph.Eur./JP		0.895 mg	0.0895 mg
Sodium acetate trihydrate	USP/Ph.Eur./JP		0.353 mg	0.0353 mg
Sodium hydroxide	NF/Ph.Eur./JP	pH adjustment	q.s. to pH 5.0	q.s. to pH 5.0
Glacial acetic acid	USP/Ph.Eur./JP	pH adjustment	q.s. to pH 5.0	q.s. to pH 5.0
Water for Injection	USP/Ph.Eur.	Solvent	q.s. to 1.0 mL	q.s. to 0.1 mL

[a] Based on the label claim, does not reflect the overfill.
[b] Actual quantity adjusted based on drug substance assay to achieve 150 mg/mL pegcetacoplan.
NF- National Formulary; USP - United States Pharmacopoeia; Ph.Eur. - European Pharmacopoeia; JP – Japanese Pharmacopoeia

2.4 Comments on Novel Excipients

- Per FDA inactive ingredient database, trehalose dihydrate has not been formerly qualified for intravitreal injection. The nonclinical studies performed by the Applicant used the clinical formulation with no toxicity associated with the vehicle.

2.5 Comments on Impurities/Degradants of Concern

Drug substance related impurities

The Applicant proposes the following specifications for the pegcetacoplan drug substance.

Table 1: Specification for Pegcetacoplan

Test Attribute	Method Type	Acceptance Criteria
Appearance	Visual	(b) (4)
Identification	MALDI TOF-MS	
Identification	RP-HPLC	
APL-2 Assay	RP-HPLC	
Purity	RP-HPLC	
Related Substances	RP-HPLC	
Related Substances	SE-HPLC	
Related Substances	SCX-HPLC	

The proposed specifications for the related substances: high molecular weight (HMW), (b) (4) are above ICH qualification limits for the drug product. The Applicant conducted two dedicated nonclinical studies (21CATX-002 and19CATX-003) in rabbits and cynomolgus monkeys to qualify the impurities. No additional toxicity was associated with formulations of Syfovre containing the impurities at levels higher than those specification proposed by the Applicant. The impurities are considered qualified for the formulation.

Specified Impurity (method)	Highest Level Observed in Nonclinical Studies	Level Qualified in Nonclinical Studies	Highest Level Observed in Clinical Studies	Proposed Commercial Limit in:	
				Drug Substance	Drug Product
(b) (4)					(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

Syfovre is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD). The recommended dose for Syfovre is 15 mg (0.1 mL of 150 mg/mL solution) administered by a single intravitreal injection to each affected eye once every (b) (4)

3 Studies Submitted

3.1 Studies Reviewed

Primary Pharmacology

- Study 18XTPH-001: Isothermal titration calorimetry: C3 and C3b
- Study 19CFPH-001: APL-2 and APL-9 inhibition of alternative and classical pathway complement activation

Secondary Pharmacology

- Study 21AWPH-001: GenomeQuest APL-2 sequence search

Safety Pharmacology

- Study 13ZTX-001: In vitro effect of APL-2 and PEG40 on hERG current (IKr) expressed in human embryonic kidney (HEK) cells

- Study 13CATX-005: A cardiovascular and respiratory safety pharmacology assessment of APL-2 given by subcutaneous injection in telemetered cynomolgus monkey

Pharmacokinetics

- Study 17MTX-001a,b,c: Pharmacokinetics, excretion, and tissue distribution of radioactivity in male cynomolgus monkeys administered a single subcutaneous or intravitreal dose of [3H]APL-2 4.2.3 Toxicology

Toxicology

- Impurity qualification
  - Study 21CATX-002: A multiple dose (2 doses 4 weeks apart) study to qualify specific degradants in intravitreally-administered heat-degraded pegcetacoplan (APL-2) to New Zealand White rabbits
  - Study 19CATX-003: A 28-day subcutaneous injection toxicity study comparing heat-degraded and non-degraded pegcetacoplan drug product in cynomolgus monkey
- Systemic toxicity
  - Study 15CATX-003: A 6-month repeat dose toxicity study of APL-2 by subcutaneous injection in New Zealand White rabbits
  - Study 15CATX-004: A 9-month repeat dose toxicity study of APL-2 by subcutaneous injection in cynomolgus monkeys with a 13-week interim necropsy
- Ocular toxicity
  - Study 14CTX-001: A 9-month ocular toxicity study of APL-2 in cynomolgus monkeys

3.3 Previous Reviews Referenced

- NDA 215014 (Orig1s000): Integrated Review; see Action Package dated 5/17/2021 (Carlaveva Thompson).

4 Pharmacology

Mechanism of Action: (excerpted from Empaveli® labeling)

Pegcetacoplan binds to complement protein C3 and its activation fragment C3b, thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation.

Reviewer's note: The Applicant's proposed labeling for Syfovre also contains the following statement: (b) (4)

(b) (4)

4.1 Primary Pharmacology

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

Human biochemical, genetic, and clinical lines of evidence indicate that the complement system plays a role in the etiology of age-related macular degeneration (AMD). Complement components including C3, the membrane-attack complex (MAC) complex, and Complement Factor H (CFH), are present in drusen and basal laminar deposits in eyes from patients with AMD. Genetic variants of CFH, C3, CFI and other complement components have been associated with altered risks for the development of both the exudative and atrophic forms of AMD. Patients with AMD also have signs of systemic complement activation, exhibiting higher serum levels of Factor B, C3a, C5a, SC5b-9, C3d, and Ba compared to age-matched controls. In addition, data from clinical trials in which complement inhibitors were used to treat AMD showed that these inhibitors may have therapeutic benefits.

Study 18XTPH-001: Isothermal titration calorimetry: C3 and C3b

Excerpted from Integrated Review of NDA 215014:

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

Pegcetacoplan Binding and Stoichiometry to C3 and C3b

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

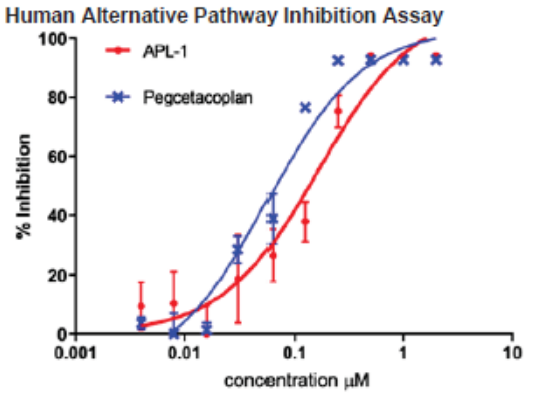
Source: Study Report 1XTPH-001, Table 1.
Abbreviations: K_d, binding constant; N, binding stoichiometry

Study 19CFPH-001: APL-2 and APL-9 inhibition of alternative and classical pathway complement activation

Excerpted from Integrated Review of NDA 215014:

> *The complement inhibitory activity of pegcetacoplan was investigated against both the classical and alternative activation pathways. The inhibitory activities of pegcetacoplan against the classical and alternative pathways were similar (half-maximal effective concentration [EC_{50}] 136nM versus 64nM). When the inhibitory*

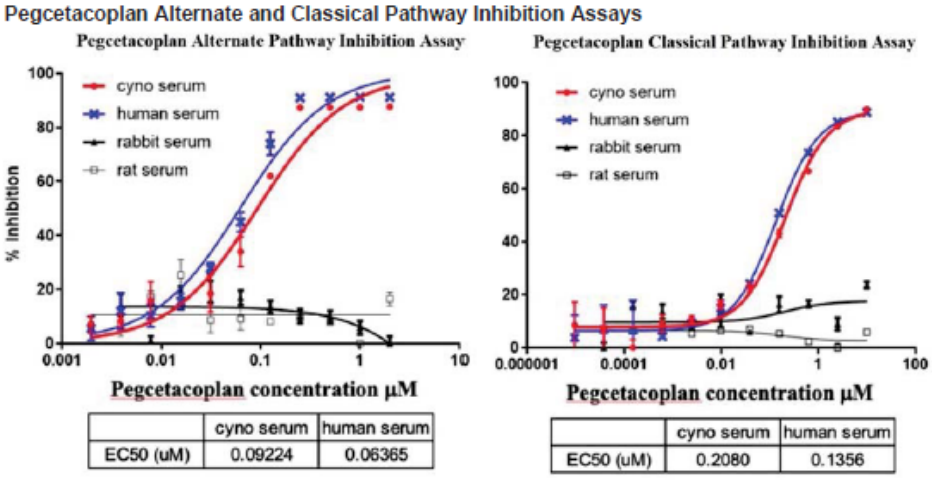
effect of pegcetacoplan was compared to a non-PEGylated version of the peptide (APL-1), PEGylation was found to shift the inhibitory dose-response curve minimally to the left (pegcetacoplan EC_{50} 57nM versus APL-1 EC_{50} 165nM).



	APL-1	Pegcetacoplan
EC50 (uM)	0.1648	0.05695

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

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



	cyno serum	human serum
EC50 (uM)	0.09224	0.06365

	cyno serum	human serum
EC50 (uM)	0.2080	0.1356

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

4.2 Secondary Pharmacology

Study 21AWPH-001: GenomeQuest APL-2 sequence search

- The peptide sequence within pegcetacoplan was queried in GenomeQuest according to the following search parameters, to identify sequence similarities

with existing proteins or peptides that could indicate a risk of cross-reactivity or biological interactions associated with those proteins or peptides:
    - GenePast Algorithm (Patent and Non-Patent results)
    - Subject Length was limited to between 3-100,000 amino acids
    - 70% Identity to Subject or Query
- The query revealed no similarity in proteins or peptide sequences, natural or artificial, in humans or otherwise, supporting a low probability for cross-reactivity of pegcetacoplan against natural receptors or ligands.

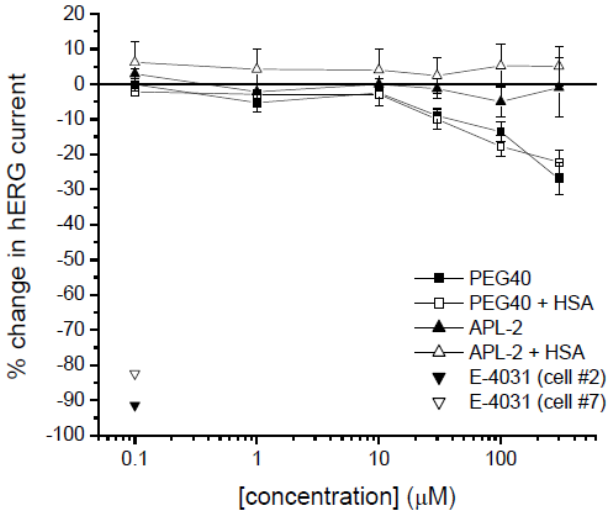
4.3 Safety Pharmacology

Excerpted from Integrated Review of NDA 215014:

Cardiovascular and respiratory safety assessments of pegcetacoplan were conducted in cynomolgus monkeys. Single doses up to 140 mg/kg and a dose of 112 mg/kg PEG-40 did not result in treatment-related changes in cardiovascular or respiratory parameters in conscious monkeys. Furthermore, pegcetacoplan had no effect on hERG current amplitude in vitro. A dedicated central nervous system safety pharmacology study was not conducted. A tissue distribution study showed that pegcetacoplan was below the level of quantitation following a single dose to monkeys, indicating a minimal risk of acute AEs on the central nervous system.

Study 13ZTX-001: *In vitro* effect of APL-2 and PEG40 on hERG current (IKr) expressed in human embryonic kidney (HEK) cells

- This study determined the hERG ion channel-blocking profile of APL-2 and PEG40 in a stably transfected human embryonic kidney (HEK 293) cell line expressing the hERG mRNA.
- APL-2 and PEG40 were examined in the absence and in the presence of human serum albumin at concentrations ranging from 1µM to 300µM at physiological temperature.
- PEG40 was associated with a modest amount of hERG current reduction reaching a 27% mean reduction at the highest concentration tested (300µM).
- APL-2 was not associated with any meaningful reduction in hERG current amplitude over the concentration range examined (1.0 ± 8.5 reduction at 300µM).
- In the presence of 4% HSA, to characterize the effects of protein binding, there was very little change in the effects of either PEG40 or APL-2 on hERG current amplitude as compared to the absence of HAS.



Study 13CATX-005: A cardiovascular and respiratory safety pharmacology assessment of APL-2 given by subcutaneous injection in telemetered cynomolgus monkey

- This study determined the potential effects of APL-2 on the cardiovascular and respiratory systems.
- Eight telemeterized cynomolgus male monkeys were administered a single subcutaneous dose of 112 mg/kg PEG40 on Day 1. On Day 15, animals were crossed-over and received either 28 (n=4) or 140 mg/kg APL-2 (n=4).
- Mortality, clinical signs, body weights were monitored. Cardiovascular, respiratory and temperature assessments, including arterial pressures, ECG waveforms, respiratory electrical impedance waveforms, and core body temperatures were collected telemetrically for baseline and post-dose on Days 1, 8, 15, and 23. Baseline assessments were conducted for approximately 18 to 24 hours. During the study period, on dosing days, data collection began 2 hours post-dose, and continued for 24 hours following the completion of dosing (Days 1 and 15). On Days 8 and 23, continuous data collection occurred for 26 hours and mimicked the start and stop times on dosing days. ECG data collection occurred at 2 and 0.5 hours prior to dosing and 1, 4, 8 and 24 hours post-dose on Days 1 and 15. Toxicokinetic samples were collected on Days 1 and 15 prior to dose, and on Days 9 and 23 at the completion of telemetry assessments. Average APL-2 serum concentration measured on Day 23 was 262 µg/mL and 628 µg/mL for the animals administered 28 and 140 mg/kg APL-2, respectively.
- Subcutaneous administrations of APL-2 (up to 140 mg/kg) or PEG40 (112 mg/kg) were without effects on body temperature, or on hemodynamic, electrocardiographic or respiratory parameters.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study 17MTX-001 a,b,c: Pharmacokinetics, excretion, and tissue distribution of radioactivity in male cynomolgus monkeys administered a single subcutaneous or intravitreal dose of [^{3}H]APL-2

- This study determined the pharmacokinetics, rates and routes of excretion, and tissue distribution of radioactivity via quantitative whole body autoradiography, following a single subcutaneous (SC) or bilateral intravitreal (IVT) dose of [^{3}H]APL-2, in male cynomolgus monkeys.
- Male cynomolgus monkeys received either a single subcutaneous injection (7mg/kg) or a single, bilateral intravitreal injection (12.4 mg/eye).
- Blood, urine, feces and cage residue were collected at designated time points up to 504 hours post-dose for radioactivity analysis from one group per treatment (n=3/group) while another group of animals from each treatment were sacrificed at up to 504 hours for collection of terminal blood and carcass/eyes for quantitative whole body autoradiography (n=5/group).
- In monkeys receiving a subcutaneous dose of 7.0 mg/kg [^{3}H]APL-2, the Tmax in serum was observed at 48 hours post-dose. The peak concentration or Cmax was 41,700.00 ± 5,759.26 ng-eq/g. The Cmax was followed by a steady gradual decline through 504 hours (3 weeks) post-dose. The final serum concentration observed at 504 hours post-dose was 6,572.92 ng-eq/g.
- In monkeys receiving an intravitreal dose of 12.4 mg [^{3}H]APL-2 per eye, the Tmax in serum was observed at 120 hours post-dose. The peak concentration or Cmax was 20,215.47 ± 4,052.63 ng-eq/g. The Cmax was followed by a slow and gradual decline through 504 hours post-dose (3 weeks). The final serum concentration observed at 504 hours post-dose was 6,335.64 ng-eq/g.
- For monkeys receiving a SC dose, the major route of elimination was urinary excretion. The mean urinary recovery of the radioactive dose through 504 hours (3 weeks) post-dose was 44.55%. Approximately 52.77% of the total dose recovered from the urine was recovered within the first 48 hours post-dose, and approximately 80.11% of the total dose recovered from the urine was recovered within the first 168 hours (1 week) post-dose. Mean total fecal recovery was 3.83 %.
- For monkeys receiving an intravitreal dose, the major route of elimination was also urinary excretion. The mean urinary recovery of the radioactive dose through 504 hours (3 weeks) post-dose was 66.58. Approximately 23.66% of the total dose recovered from the urine was recovered within the first 48 hours post-dose, and approximately 66.48% of the total dose recovered from the urine was recovered within the first 168 hours (1 week) post-dose. Mean total fecal recovery was 8.12%.
- Following SC administration, the drug-derived radioactivity was widely distributed. The Cmax for distribution was observed at 72 hours for 19 of 37 tissues analyzed.
    - Distribution was either not observed or below the limit of quantitation (BLQ) in the following tissues: central nervous system (including cerebellum, cerebrum, medulla, and spinal cord), bone, fat (white), large intestinal contents, optic nerve, small intestinal contents, and stomach

contents. Radioactivity was observed within the walls of the gastrointestinal tract as a result of normal blood circulation. There was no appreciable distribution to the eye.
    - 25 of 37 tissues analyzed had quantifiable levels of radioactivity. The tissues, listed from highest to lowest concentration (at the 8-hour timepoint), included: SC dose site; urine; blood; lung; kidney; liver; spleen; adrenal gland; pancreas; myocardium; fat, brown; salivary gland; bone marrow; small Intestine; lacrimal gland; large intestine; cecum contents; stomach; thymus; thyroid gland; cecum; diaphragm; lymph node; skin; and eye.
- Following an intravitreal administration, the drug-derived radioactivity was widely distributed. The Cmax for distribution was observed at 24 hours for 17 of 38 tissues analyzed.
    - Distribution was either not observed or below the limit of quantitation (BLQ) in the following tissues: central nervous system (including cerebellum, cerebrum, medulla, and spinal cord), bone, fat (white), small intestinal contents, and stomach contents, large intestinal contents, diaphragm, epididymis, skin, or lymph Node.
    - 23 of 38 tissues analyzed had quantifiable levels of radioactivity. The tissues, listed from highest to lowest concentration (at the 8-hour timepoint), included: eye; urine; lung; blood; kidney; adrenal gland; liver; lacrimal gland; spleen; pancreas; small intestine; bone marrow; cecum; salivary gland; myocardium; stomach; large intestine; thyroid gland; fat, brown; thymus; skin; prostate gland; and large intestinal contents. At the terminal timpoint (Hour 504), significant radioactivity was remained in the eye.
- The right eyes were removed and embedded separately for QWBA analysis. Quantifiable levels of radioactivity were observed in several ocular tissues within the eye, including (listed from highest concentration to lowest, over time): vitreous humor, aqueous humor, cornea, and lens. Radioactivity was also observed in the optic nerve at 288 and 504 hours postdose.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Systemic toxicity:

Systemic toxicity of pegcetacoplan (APL-2) was previously reviewed for approval of NDA 215014 including:

- Study 15CATX-003: A 6-month repeat dose toxicity study of APL-2 by subcutaneous injection in New Zealand White rabbits
- Study 15CATX-004: A 9-month repeat dose toxicity study of APL-2 by subcutaneous injection in cynomolgus monkeys with a 13-week interim necropsy

The following are excerpted from the Integrated Review of NDA 215014:

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

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

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

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

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

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

Whether the tubular degeneration is secondary to vacuolation or occurs by another mechanism, the lack of elevation in serum blood urea nitrogen and creatinine suggests that renal function is not notably impaired by this histological change to the tubules despite chronic exposure…The no observed adverse effect level (NOAEL) for renal tubular degeneration was at 7 mg/kg.

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

Of relevance to the choroid plexus, Fletcher reported sheets of vacuolated macrophages that disrupted the interstitium of the choroid plexus of monkeys at a PEG-40 load of ~160 mg/kg per week, which is appropriately considered an AE on tissue structure. Monkeys administered 7 and 28 mg/kg/d were exposed to a weekly PEG-40 load of ~44 mg/kg and 176 mg/kg for 9 months… Vacuolation of the choroid plexus epithelium was observed at a similar incidence at both doses but with greater severity (to moderate) at the higher 28 mg/kg dose. There was no reported evidence of disrupted tissue structure (e.g., degeneration/ regeneration, necrosis, hyperplasia, interstitial expansion, etc.) of the choroid plexus itself or of the surrounding vasculature and brain tissue at either dose. There was also no adverse clinical signs indicative of neurobehavioral disruption, at least from routine observation in the pivotal toxicology studies…Clinical exposure to pegcetacoplan is concluded to be within an acceptable range of nonadverse exposure to PEG-40.

Study title: A multiple dose (2 doses 4 weeks apart) study to qualify specific degradants in intravitreally-administered heat-degraded pegcetacoplan (APL-2) to New Zealand White rabbits

Study no.:	21CATX-002
Study report location:	\\CDSESUB1\evsprod\nda217171\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\21catx-002\21catx-002.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	4-16-2021
GLP compliance:	Yes
QA statement:	Yes; signed
Drug, lot #, and % purity:	APL-2: Lot#028678, 99.8% purity Heat-degraded APL-2: Lot#028678, 96.7% purity

Methods

Doses:	Vehicle APL-2: 15 mg/eye Heat-degraded APL-2: 15 mg/eye
Frequency of dosing:	2 injections separated by 20 minutes
Route of administration:	Intravitreal injection; bilateral
Dose volume:	0.05 mL (150 mg/mL) x 2 injections (separated by 20 minutes) on Day 1 and Day 30
Formulation/Vehicle:	(b) (4)
Species/Strain:	Rabbit / New Zealand White
Number/Sex/Group:	6 males / group
Age:	4-months
Weight:	2.1 – 2.7 kg
Unique study design:	This study was designed to determine differences in the ocular toxicity of APL-2 drug product and a formulation of APL-2 which underwent heat degradation. The study was conducted to qualify impurities in the drug product to the proposed specifications. See below for impurity content of the heat degraded product.
Deviation from study protocol:	None of the deviations were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions

Observations and Results

Mortality (twice daily)

- No animals died or were sacrificed moribund prior to schedule.

Clinical Signs (Cageside: twice daily; Detailed: weekly)

- Individual animal findings:
  - Partially closed eyes
    - Animal 2002
      - Days 2 (right eye only), 35 (left eye only), and 40 (right eye only)
      - Animal also presented with red coloration of the left eye from Day 35 through the end of the study on Day 60.
      - Considered to be related to the clinical condition of the eyes either from the dosing procedure (Day 2) or associated with the more chronic redness that developed starting Day 35.

Body Weights (weekly)

- No changes in body weights or body weight gain attributed to the test article.

Feed Consumption (quantitative; daily)

- No changes in feed consumption attributed to the test article.

Ophthalmoscopy (Slit Lamp and Funduscopy; Pre-study and Days 3, 7, 14, 21, 28, 32, 39, 46, 53, 60 (prior to necropsy)

- Vitreal cell; anterior (very slight – slight)
  - 9/12 APL-2-treated eyes and 10/12 Heat-Degraded APL-2-treated eyes
  - Incidence and severity were similar between both groups and the incidence increased following the second dose administration on Day 30.
  - These findings were considered test item-related and non-adverse.
- Individual animal findings
  - Animal No. 2002 (APL-2)
    - The left eye developed prominent inflammation, with changes noted following the second dose administration of APL-2 on Day 30.
    - Anterior chamber cells, flare and fibrin, cell-like opacities on the anterior lens capsule, iris swelling and hyperemia, incomplete pupil dilation, fundus hazy or limited view, vitreal opacities and cells, retinal elevation and hemorrhage were noted. Most of these changes remained present on on Day 60.
    - A posterior lens capsule rupture was suspected during the last two observations (Days 53 and 60).
    - These changes correlated with the eye redness observed during the clinical observations (see above) and were likely test item-related. Procedure-related aspects cannot be entirely ruled out due

to the low incidence and that the changes were unilateral in this animal.

- Animal No. 3002
  - Corneal ulcer in the left eye secondary to the dosing procedure.
  - Corneal opacity, edema, and vascularization were observed secondary to the ulcer.
  - A minor eyelid blepharoplasty procedure was performed to allow for corneal healing (blepharospastic entropion preventing corneal epithelial healing).

Tonometry (Prestudy and Days 3, 7, 14, 21, 28, 32, 39, 46, 53, 60 (prior to necropsy)

- No changes in intraocular pressure attributed to the test article.

Electroretinography (Scotopic / Photopic; prestudy and approximately 5 days post each dose and within 3 days of necropsy)

- No changes in ERG parameters attributed to the test article.

Spectral Domain Optical Coherence Tomography (dilated; prestudy and approximately 7 days post each dose and within 3 days of necropsy)

- No changes in retinal morphology attributed to the test article.

Hematology

- Decreased reticulocyte count (minimal)
  - APL-2
    - 0.84x group mean compared to control
    - This change was not associated with changes in red blood cell counts and was within the background range for New Zealand White rabbits.

Clinical Chemistry

- No changes in clinical chemistry parameters attributed to the test article.

Gross Pathology

- No macroscopic observations attributed to the test article.

Organ Weights

- Increased adrenal gland weight
  - Heat-Degraded APL-2
    - Increase of 30%, 26% and 30% in absolute, relative to body, and relative to brain weight, respectively.
    - Correlated microscopically with minimal to mild cortical hypertrophy and was considered to be likely secondary to stress.

- Individual Animal Findings
    - Animal No. 2002 (APL-2)
        - Similar mild increase in adrenal gland weight was noted.

Histopathology

Adequate Battery: Standard systemic tissue battery; five sagittal sections of each eye prepared

Peer Review: No.

Histological Findings

- Vitreous body: mononuclear cell infiltrate (minimal – mild)
    - APL-2
        - 6/12 eyes
    - Heat-degraded APL-2
        - 7/12 eyes
    - Mainly composed of vacuolated (foamy) macrophages with fewer small lymphocytes.
    - Correlated clinically with vitreous opacities (cell-like) observed during the ophthalmology examinations.
- Optic disc: mononuclear cell infiltrate (minimal – mild)
    - APL-2
        - 5/12 eyes
    - Heat-degraded APL-2
        - 6/12 eyes
    - Characterized as vacuolated (foamy) macrophages
- Adrenal glands: cortical hypertrophy, bilateral diffuse (minimal to mild)
    - Observed in animals administered Heat-Degraded APL-2 and animal No. 2002 given APL-2.
    - Correlated with an increased adrenal gland weight in the above-mentioned animals and was considered likely secondary to stress.

- Individual animal findings:
    - Animal 2002 (APL-2)
        - The left eye of animal No. 2002 given APL-2 had moderate vitreous (mostly ventral) and optic disc infiltration with additional mild vitreous/retina fibroplasia (with secondary lens capsule rupture, traction on retina and optic disc, and retinal detachment) and moderate choroid mononuclear cell infiltrates (mainly lymphocytic). Mild axonal degeneration was observed in the optic nerve of this eye and throughout the visual pathways in the brain. This was considered secondary to the intraocular optic disc traction. Even though this eye was an outlier in the study in terms of severity grades and additional changes (i.e., fibroplasia and choroid moderate infiltration), the high amount of vacuolated macrophages present in the vitreous was suggestive of a direct effect of APL-2.

Dosing Solution Analysis

- APL-2:
  - No significant differences in results were observed between the post-study retained samples and the post-study residual samples.
- Heat degraded APL-2:
  - No significant differences in results were observed between the post-study retained samples and the post-study residual samples. The pre-study results were similar to the post-study results with one exception: the pre-study results showed elevated levels of the high molecular weight (HMW) degradation product compared to the levels observed in the post-study samples (2.8 wt.% HMW was observed pre-study compared to 2.2 wt.% observed in the post-study retained samples by SE-HPLC analysis).

Degradation products observed for heat-degraded APL-2 (b) (4) drug product (Lot 028678)

High Molecular Weight (HMW)	2.8%
(b) (4)	

Conclusion:

- Intravitreal administration of APL-2 (Pegcetacoplan) or Heat-Degraded Pegcetacoplan (APL-2) on Days 1 and 30 was generally well tolerated in rabbits at dose levels of 15 mg/eye.
- There were no observations in Heat Degraded APL-2 dosed eyes that were more marked than in APL-2 dosed eyes. The degradations products are qualified to the minimum value noted in the dosing solution analysis.
- One APL-2 treated eye developed moderate inflammation following the second dose. It remains uncertain if there was a procedural related inflammatory response or if a direct APL-2 related effect was involved**.**

Study title: A 28-day subcutaneous injection toxicity study comparing heat-degraded and non-degraded pegcetacoplan drug product in cynomolgus monkey

Study no.:	19CATX-003
Study report location:	\\CDSESUB1\evsprod\nda217171\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\19catx-003\19catx-003.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	3-16-2020
GLP compliance:	Yes
QA statement:	Yes; signed
Drug, lot #, and % purity:	Pegcetacoplan: Lot#2554-107, 99.7% purity Pegcetacoplan (heat-degraded): Lot#2554-107, 99.4% purity

Key Study Findings

Methods

Doses:	Vehicle Pegcetacoplan: 28 mg/kg/day Pegcetacoplan (heat-degraded): 28 mg/kg/day
Frequency of dosing:	Once daily for 28 days
Route of administration:	Subcutaneous injection
Dose volume:	1.5 mL/kg
Formulation/Vehicle:	(b) (4)
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	3/sex/group
Age:	2.6 – 3.6 years
Weight:	1.7 – 2.8 kg
Unique study design:	This study was designed to determine differences in the systemic toxicity of the pegcetacoplan drug substance and pegcetacoplan which underwent heat degradation. The study was conducted to qualify impurities in the drug product to the proposed specifications. See below for impurity content of the heat degraded product.
Deviation from study protocol:	

Observations and Results

Mortality

- No animals died or were sacrificed moribund prior to schedule.

Clinical Signs

- No changes in clinical signs attributed to the test articles.

Body Weights

- No changes in body weights attributed to the test articles.

Feed Consumption

- No changes in feed consumption attributed to the test articles.

Ophthalmoscopy

- No changes in ophthalmologic observations attributed to the test articles.

ECG

- No changes in ECG parameters attributed to the test articles.

Hematology

- Day 29
  - Red cell mass (red blood cell count [RBC], hemoglobin concentration [Hgb] and hematocrit [Hct]) decreased
    - Minimal
    - Occurred in both non-degraded and heat-degraded pegcetacoplan groups with a similar, but less pronounced effect was observed in the vehicle control group.

Fold Change in Group Mean Hematology Parameters Associated with Administration of Pegcetacoplan to Cynomolgus Monkeys for 28 Days

Sex	Male			Female		
Treatment	Group 1 (Control)	Group 2 (Non-Degraded Pegcetacoplan)	Group 3 (Heat-Degraded Pegcetacoplan)	Group 1 (Control)	Group 2 (Non-Degraded Pegcetacoplan)	Group 3 (Heat-Degraded Pegcetacoplan)
Dose Level (mg/kg/day)	0	28	28	0	28	28
Parameter						
RBC	0.91x	0.89x	0.86x	0.91x	0.88x	0.84x
Hgb	0.92x	0.89x	0.85x	0.91x	0.89x	0.84x
Hct	0.90x	0.90x	0.86x	0.88x	0.89x	0.82x

"X" represents mean fold change compared to prestudy values.

- No effects on coagulation were observed.

Clinical Chemistry

- Day 29
  - Cholesterol (Chol) decreased
    - Graded minimal to mild
    - Occurred in in both non-degraded and heat-degraded pegcetacoplan groups
  - Potassium (K) decreased
    - Minimal

- Occurred in heat-degraded pegcetacoplan dosed males. A similar, but less pronounced change for potassium was noted in Vehicle Control males and females.

Fold Change in Group Mean Clinical Chemistry Parameters Associated with Administration of Pegcetacoplan to Cynomolgus Monkeys for 28 Days

Sex	Male			Female		
Treatment	Group 1 (Control)	Group 2 (Non-Degraded Pegcetacoplan)	Group 3 (Heat-Degraded Pegcetacoplan)	Group 1 (Control)	Group 2 (Non-Degraded Pegcetacoplan)	Group 3 (Heat-Degraded Pegcetacoplan)
Dose Level (mg/kg/day)	0	28	28	0	28	28
Parameter						
Chol	0.98x	0.82x	0.76x	0.99x	0.80x	0.76x
K	0.91x	0.83x	0.79x	0.87x	1.01x	0.85x

"X" represents mean fold change compared to prestudy values.

Gross Pathology

- No changes in macroscopic findings attributed to the test articles.

Organ Weights

- No changes in organ weights attributed to the test articles.

Histopathology

Adequate Battery: Yes.

Peer Review:

Histological Findings:

- The infiltrates of histiocytes seen at the administration sites contained variable sized vacuoles in the cytoplasm as described below and the minimal granulomatous inflammation were considered related to the administration of the pegcetacoplan drug products.
- Findings of minimal to mild vacuolation of macrophages in the lymph nodes and spleen, minimal infiltrates of histiocytes containing variable sized vacuoles in the cytoplasm in the choroid plexus of the brain, and minimal tubular vacuolation or minimal tubular degeneration/regeneration in the kidneys were observed in the groups dosed with the pegcetacoplan drug products. These findings were consistent with the microscopic findings seen in prior systemic toxicity studies conducted for NDA 215014 (see summary of systemic toxicity above). The tubular degeneration/regeneration in the kidney was considered adverse. All other findings were considered non-adverse because findings were minimal to mild in severity and were not associated with degenerative tissue changes.

Summary of Microscopic Findings – Terminal Euthanasia (Day 29)

	Males			Females		
Group	**1**	**2**	**3**	**1**	**2**	**3**
Dose (mg/kg/day)	**0**	**28**	**28**	**0**	**28**	**28**
No. Animals Examined	**3**	**3**	**3**	**3**	**3**	**3**
Administration site 1-7[b]						
Fibrosis	(2)[a]	(8)	(7)	(4)	(9)	(5)
Minimal	2	7	6	4	8	5
Mild	0	1	1	0	1	0
Hemorrhage	(0)	(2)	(4)	(1)	(3)	(1)
Minimal	0	2	2	1	2	1
Mild	0	0	2	0	1	0
Inflammation, granulomatous	(0)	(0)	(1)	(0)	(0)	(0)
Minimal	0	0	1	0	0	0
Infiltrate, mononuclear cell	(0)	(0)	(0)	(3)	(0)	(0)
Minimal	0	0	0	3	0	0
Infiltrate, mixed cell	(0)	(1)	(1)	(1)	(1)	(0)
Minimal	0	1	0	1	1	0
Mild	0	0	1	0	0	0
Infiltrate, histiocytic	(0)	(16)	(11)	(0)	(13)	(15)
Minimal	0	16	11	0	13	15
Draining lymph nodes (axillary and/or iliac)[b]						
Vacuolation, macrophage	(0)	(4)	(3)	(0)	(4)	(3)
Minimal	0	2	2	0	1	2
Mild	0	2	1	0	3	1
Lymph node, mandibular						
Vacuolation, macrophage	(0)	(2)	(3)	(0)	(2)	(2)
Minimal	0	2	3	0	2	2
Lymph node, mesenteric						
Vacuolation, macrophage	(0)	(3)	(1)	(0)	(1)	(3)
Minimal	0	1	1	0	1	2
Mild	0	2	0	0	0	1
Kidney						
Degeneration/regeneration, tubular	(0)	(1)	(1)	(0)	(1)	(0)
Minimal	0	1	0	0	1	0
Mild	0	0	1[c]	0	0	0
Vacuolation, tubular	(0)	(0)	(1)	(0)	(0)	(0)
Minimal	0	0	1	0	0	0

	Males			Females		
Group	**1**	**2**	**3**	**1**	**2**	**3**
Dose (mg/kg/day)	**0**	**28**	**28**	**0**	**28**	**28**
No. Animals Examined	**3**	**3**	**3**	**3**	**3**	**3**
Brain						
Infiltration, histiocytic, choroid plexus	(0)	(1)	(0)	(0)	(2)	(2)
Minimal	0	1	0	0	2	2
Spleen						
Vacuolation, macrophage	(0)	(1)	(2)	(0)	(3)	(2)
Minimal	0	0	2	0	3	2
Mild	0	1	0	0	0	0

[a] Numbers in parentheses represent the number of animals with the finding.
[b] Incidence combined for all administration sites and draining lymph nodes.
[c] Group 3 male 3002 discussed below.

Toxicokinetics

Summary of Pegcetacoplan Serum Concentrations (µg/mL)

Time Point	Group 1 (Vehicle Control)		Group 2 (28 mg/kg/day, Non-degraded Pegcetacoplan)		Group 3 (28 mg/kg/day, Heat-degraded Pegcetacoplan)	
	Female	Male	Female	Male	Female	Male
Day 1: Pre	BQL	BQL	BQL	BQL	BQL	BQL
Day 1: 8 hr Post	BQL	BQL	106.87	112.90	142.60	174.00
Day 2: Pre	BQL	BQL	217.00	191.00	259.33	328.67
Day 3: Pre	BQL	BQL	533.33	486.33	559.00	622.33
Day 6: Pre	BQL	BQL	1090.00	1040.67	1183.33	1166.67
Day 15: Pre	BQL	BQL	1696.67	1470.00	1666.67	1543.33
Day 15: 8 hr Post	BQL	BQL	1686.67	1646.67	1680.00	1536.67
Day 18: Pre	BQL	BQL	1773.33	1616.67	1720.00	1633.33
Day 21: Pre	BQL	BQL	1700.00	1693.33	1726.67	1746.67
Day 24: Pre	BQL	BQL	1733.33	1726.67	1780.00	1756.67
Day 28: Pre	BQL	BQL	1793.33	1643.33	1733.33	1680.00
Day 28: 8 hr Post	BQL	BQL	1870.00	1766.67	1750.00	1750.00
Day 28: 24 hr Post	BQL	BQL	1726.67	1786.67	1673.33	1740.00

BQL = below limit of quantitation.

Dosing Solution Analysis

- APL-2:
  - No significant differences in results were observed between the post-study retained samples and the post-study residual samples.
- Heat degraded APL-2: No significant differences in results were observed between the post-study retained samples and the post-study residual samples.

Degradation products observed for heat-degraded APL-2 (b) (4) drug product (Lot#2554-107)

High Molecular Weight (HMW)	2.8%
(b) (4)	

Conclusion:

- Subcutaneous administration of APL-2 (Pegcetacoplan) or Heat-Degraded Pegcetacoplan (APL-2) on Days 1 and 30 was generally well tolerated in monkeys at dose levels of 28 mg/kg/day.
- There were no observations in heat degraded APL-2 dosed monkeys that were significantly more marked than in non-heat degraded APL-2 dosed monkeys. Findings of tubular degeneration in both groups, while considered adverse following subcutaneous administration, are not considered concerning at the much lower systemic exposure resulting from intravitreal administration.

- The degradations products are qualified to the minimum value noted in the dosing solution analysis.

Study title: A 9-month ocular toxicity study of APL-2 in cynomolgus monkeys

Study no.:	Study 14CTX-001
Study report location:	\\CDSESUB1\EVSPROD\nda217171\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\14ctx-001\14ctx-001.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	3-12-2014
GLP compliance:	Yes
QA statement:	Yes; signed
Drug, lot #, and % purity:	APL-2, Batch# A2N-363-BA522-S214, 99.8% purity

Key Study Findings

- No significant toxicity was associated with intravitreal injection of APL-2; the NOAEL of the study is the high dose: 24.8 mg/eye/dose q4weeks for 9 months.

Methods

Doses:	Group 1: Vehicle control Group 2: Control article (PEG): 22.64 mg/eye/dose Group 3: APL-2 (3.1 mg/eye/dose) Group 4: APL-2 (12.4 mg/eye/dose) Group 5: APL-2 (24.8 mg/eye/dose)
Frequency of dosing:	Once every 4 weeks for 9 months
Route of administration:	Bilateral intravitreal injection
Dose volume:	Groups 1,3,4: 0.05mL/dose Groups 2, 5: 0.1mL/dose
Formulation/Vehicle:	5% dextrose
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	3/sex/group
Age:	2.3 - 3.4 years
Weight:	2.5 - 4.4 kg
Deviation from study protocol:	None which affected conduct or interpretability of results.

Observations and Results

Mortality

- No animals died or were sacrificed moribund prior to schedule.

Clinical Signs (daily)

- APL-2
  - Eye opacity
    - Attributed to injection procedure
  - Scattered finding included pupil constriction, conjunctival swelling and partial eye closure with low incidence and no apparent dose response.

Ocular Clinical Signs
(Study Day)

Animal No.	Eye Opacity	Pupil Constriction	Pupil Dilation	Periorbital Swelling	Conjunctival Swelling	Partial Eye Closure
1003	-	-	OU 79	OS 155*	-	-
2001	-	-	-	OU 198-202	-	-
3001	-	-	-	-	OS 86-87	-
4001	OD 20-22	-	-	-	-	-
4002	OD 10-22	OD 31-32	OS 10-22	-	-	-
5001	OS 59-62	-	OU 79-83	-	-	-
5501	-	-	-	-	-	OD 142

- = not applicable; OD = right eye; OS = left eye; OU = both eyes.
* Associated with bruise and abrasion.

Body Weights (weekly)

- No changes in body weight attributed to the test article.

Feed Consumption (daily; qualitative)

- No changes in feed consumption attributed to the test article.

Ophthalmoscopy (toward the end of Weeks 1, 5, 9, 12, 13, 17, 21, 25, 29, 33, 37, and 39; Slit lamp biomicroscopy and indirect ophthalmoscopy; scored using the modified Hackett McDonald scale).

- Anterior vitreous: Pigmented and nonpigmented cells
  - Occurred in all treated groups (including Group 2: Control Article) except vehicle control.
  - No dose response
  - The incidence and severity of these cells in the anterior vitreous were higher in Groups 2 (Control article) and 5 (Group 5 - APL-2: 24.8 mg/eye/dose) and was possibly related to the fact that these two groups underwent vitreous aspiration prior to IVT (due to higher administered dose volumes) dosing whereas the other groups did not. Such aspirate procedures add to the trauma effects in the posterior segment and increase the cellular response noted.
  - As the study progressed with repeated injections in all groups, the occurrence of these cells in the anterior vitreous became more uniform across all groups.
- No other changes in ophthalmologic observations attributed to the test article.

Tonometry

- No changes in intraocular pressure attributed to the test article.

Spectral domain optical coherence tomography (SD-OCT)

- No changes in the retina based on SD-OCT evaluation were attributed to the test article.

Electroretinography

- No changes in electroretinographic parameters attributed to the test article.

Hematology/Coagulation (Weeks 2, 5, 9, 13, 25, 29)

- No changes in hematological/coagulation parameters attributed to the test article.

Clinical Chemistry (Weeks 2, 5, 9, 13, 25, 29)

- No changes in clinical chemistry parameters attributed to the test article.

Gross Pathology

- No macroscopic observations attributed to the test article.

Organ Weights

- No changes in organ weights attributed to the test article.

Histopathology

Adequate Battery: Yes; standard systemic tissues examined; each eye, with optic nerve, was embedded in paraffin and sectioned parallel to the ciliary artery to include optic nerve, macula, and optic disc. After the section was faced, 5 sections (step-sectioned, with sections collected at approximate 30-micron steps) were collected.

Peer Review: No

Histological Findings

- No microscopic findings attributed to the test article.

Special Evaluation

- APL-2 was not antigenic (no anti-drug antibodies detected)

Toxicokinetics

Selected Mean (SD) Toxicokinetic Parameters for APL-2 in Cynomolgus Monkeys

Dose (mg/ eve)	T_{max}[a] (h)	C_{max} (µg/mL)	C_{max}/D (µg/mL)/(mg)	AUC_{0-t} (h × µg/ mL)	AUC_{0-inf} (h × µg/ mL)	$t_{1/2}$ (hr)
Week 1[b]						
3.1	180 (144, 206)	28.7 (6028)	4.62 (1.01)	11800 (1630)	14100 (2770)	230 (7.68)
12.4	144 (21, 216)	86.9 (22.4)	3.50 (0.905	1400 (232)	40500 (5120)	236 (50.0)
24.8	180 (144, 216)	174 (32.5)	3.50 (0.655)	70700 (9770)	89200 (1060)	205 (30.3)
Week 37[b]						
3.1	144 (144, 216)	20.4 (5.35)	3.29 (0.862)	7010 (1740)	7600 (1990)	187 (9091)
12.4	144 (144, 216)	52.3 (18.4)	2.11 (0.744)	19000 (7040)	18400 (4850)	194 (55.9)
24.8	144 (24, 216)	99.0 (32.8)	2.00 (0.662)	33900 (11600)	41400 (15300)	194 (22.0)

Abbreviations: AUC_{0-inf}, area under the concentration versus time curve from the start of dose administration extrapolated to infinity; AUC_{0-t}, area under the concentration versus time curve from the start of dose administration to the last observed quantifiable concentration; C_{max}, maximum observed concentration measured after dosing; C_{max}/D, maximum observed concentration measured after dosing divided by the dose administered; f_{inf}, extrapolated area under the concentration versus time curve from the time of the last measurable concentration to infinity; $t_{½}$, apparent terminal elimination half-life; T_{max}, time after dosing at which the maximum observed concentration was observed.

[a] median (minimum, maximum).

[b] AUC_{0-t} is 0-672 hours postdose during Week 1 and 0-624 hours postdose during Week 37.

Source: d2nca\tables\doc\14CTX-001-TK-parameters-byWeek.docx and wnl\APL2_d2nca_14CTX_001.phxproj

Dosing Solution Analysis

- In general, dosing solutions remained within 5% of nominal values. For Group 4/5 (target 248 mg/mL), concentrations ranged from 201.7924 to 245.2320 mg/mL. Relative mean standard deviation for homogeneity samples was 6.857 % relative standard deviation, which slightly exceeded the 5% acceptance criterion. All but Week 1 samples passed the criteria upon reinjection. The relative mean standard deviation for the analysis of the Week 1 back-up samples passed the acceptance criteria and the analytical variability was attributed to the viscous nature of the formulation and based on the overall analytical results, the formulations were considered to be accurate.

6 Genetic Toxicology/ Carcinogenesis

Excerpted from Integrated Review of NDA 215014:

> *The carcinogenic potential of pegcetacoplan was not investigated in rodents because of the lack of pharmacological activity in species other than humans and monkeys. Suppression of complement activation is not known to be directly associated with carcinogenic signaling pathways (Hanahan and Weinberg 2011), and no histological findings interpreted as preneoplastic were observed in the toxicology studies conducted in monkeys. Pegcetacoplan is considered nongenotoxic based on results from in vitro and in vivo genotoxicity tests.*

9 Reproductive and Developmental Toxicology

- Review of the reproductive toxicity studies was previously performed for NDA 215014 (Empaveli®; Applicant's data). The following excerpts from the Integrated Review summarize these results:

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

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

Maternal pegcetacoplan exposure increased less than dose-proportionally on GD 111 relative to GD 48. After giving birth, maternal pegcetacoplan levels decreased over time and were quantifiable until postpartum day (PPD) 14 and PPD 28 at 7 and 28 mg/kg, respectively. Serum levels in infants were quantifiable on birth day (BD), 14, 28, 91, and 182. Maternal milk pegcetacoplan levels were detectable at 7 and 28 mg/kg up to PPD 14. Pegcetacoplan concentrations in maternal milk were <1 % of the plasma levels. The number of infants per group (9) was consistent with that recommended in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use S6(R1) to allow sufficient evaluation of postnatal development in monkeys.

- Exposure margins calculated for labeling:
  - LOAEL (abortions and stillbirths): 28 mg/kg/day
    - Monkey AUC at 28 mg/kg/day (GD28): 44300 µg·hr/mL
    - Human AUC at 15 mg/month IVT: 43.4 µg·hr/mL
    - Exposure margin: 1020-fold
  - NOAEL: 7 mg/kg/day
    - Monkey AUC at 7 mg/kg/day (GD28): 20500 µg·hr/mL
    - Human AUC at 15 mg/month IVT: 43.4 µg·hr/mL
    - Exposure margin: 472-fold

11 Integrated Summary and Safety Evaluation

Toxicity	Species	NOAEL (mg/eye)	Safety Margin Based on Vitreal Volume*
No adverse toxicity	Monkey	28.4 mg/eye (14.2 mg/mL vitreous)	3.78-fold

*based on human dose of 15 mg/eye and monkey dose of 28.4 mg/eye normalized to vitreous volumes of 4mL and 2mL for the human and monkey, respectively.

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/s/

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10/27/2022 08:43:14 PM

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10/27/2022 09:36:04 PM
I concur