CENTER FOR DRUG EVALUATION AND RESEARCH

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:	217225
Supporting document/s:	SD #1 - Clinical Information SD #4 - Nonclinical Information SD #5 - New NDA/CMC Information
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Product:	IZERVAY (Avacincaptad Pegol) Solution for Intravitreal Injection
Indication:	Treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)
Applicant:	IVERIC bio, Inc
Clinical Division:	Division of Ophthalmology
Pharm/Tox Division:	Division of Pharm/Tox for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/ Specialty Medicine (DPT-RPURM/SM)
Reviewer:	María I. Rivera, PhD
Supervisor/Team Leader:	Kimberly P. Hatfield, PhD (acting for Lori E. Kotch, PhD, DABT)
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Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

IVERIC bio has submitted this 505(b)(1) application for the marketing authorization of avacincaptad pegol for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD). Avacincaptad pegol (also referred to by the Applicant as ARC1905 or Zimura) is a polyethylene glycol (PEG)-conjugated RNA aptamer. RNA-based aptamers are chemically synthesized small molecules not derived from biological systems. Avacincaptad pegol is an inhibitor of complement activation that acts by binding to human complement component 5 (C5) with high affinity and specificity. Avacincaptad pegol has demonstrated complement inhibitory activity in several in vitro and ex vivo functional assays and in vivo in the monkey. The intended clinical dose is 2 mg, administered by intravitreal (IVT) injection once per month.

1.2 Brief Discussion of Nonclinical Findings

Repeat-dose IVT toxicity studies were conducted in New Zealand White rabbits (0, 0.15, 0.5, and 1.5 mg/eye) and Beagle dogs (0, 0.3, 1, and 3.0 mg/eye). The studies included a combination arm of the high dose plus Lucentis® (ranibizumab for IVT injection), a recombinant humanized monoclonal antibody that binds and inhibits vascular endothelial growth factor (VEGF). The main finding in both species was vacuolation of the ganglion cell layer of the retina observed upon microscopic evaluations. In the dog, vacuolation of the optic tract in the brain was also observed. Coadministration with Lucentis® did not impact these findings.

In the rabbit, based on the retinal vacuolation, the NOEL for avacincaptad pegol is 0.5 mg/eye for single and repeated IVT injections (0.66X the recommended clinical dose). The vacuolation was mostly of mild severity, reversible, and not associated with histopathological adverse changes (i.e., retinal degeneration, inflammation, necrosis, etc.) or noticeable effects on electroretinography (ERG) measurements. Therefore, it appears not to be adverse. In the absence of adverse effects at the doses examined, the NOAEL for avacincaptad pegol is considered to be ≥ 1.5 mg/eye (2X the recommended clinical dose).

In the dog, the finding of retinal vacuolation was observed at all dose levels (0.3 to 3 mg/eye). There was no NOEL following single or repeated IVT injections Given the more diffuse retinal vacuolation observed at 3.0 mg and extension of the finding to the optic tract, a conservative approach was used to select the NOAEL. The NOAEL is considered to be 1.0 mg/eye (0.66X the recommended clinical dose) even though optic tract vacuolation at 3.0 mg/eye was not associated with any adverse histopathology or significant ERG findings.

The presence of the vacuoles most likely reflects uptake of the PEGylated aptamer within the retinal cells (i.e., the vacuoles may occur due to the presence of the PEG polymer conjugated to the aptamer). These findings were not considered adverse as

there were no histopathology findings consistent with tissue damage or inflammation or noticeable ERG changes. These vacuolation findings were reversible or partially reversible in both species. The retinal vacuolation was not observed in the clinical trials as monitored by optical coherence tomography (OCT).

After IVT administration in NZW rabbits and beagle dogs, there were no adverse systemic effects up to the highest dose evaluated. In the dog, there were marginally increased APTT values at the high dose (ARC1905 3 mg/eye ± Lucentis 0.5 mg/eye) from Week 13 onward. The finding was not present following a 4-week recovery period. Per the Applicant, effects on coagulation (APTT and PT) were monitored in the clinic (Study OPH2000; doses of 0.3, 1, and 2 mg for at least 6 months) with no adverse effects observed.

In IV toxicity studies in rats and monkeys of up to 7-day duration, adverse effects included mortalities (attributed to cardiopulmonary failure resulting from hemorrhage and edema in the heart and lungs in monkeys), increased incidence of rouleaux formation, anemia, thrombocytopenia, hypoproteinemia, and/or various clinical chemistry changes. Vacuolation of macrophages in multiple tissues and prolongation of APTT and PT was observed in both species. Most clinical pathology findings were reversible or partially reversible. Vacuolation in macrophages was still present in multiple tissues at the end of the recovery period. A NOAEL was not identified in the 7-day IV toxicity studies. At the low dose in each study (367 mg/kg/day in rats and 141 mg/kg/day in monkeys), exposure margins are over 1000X (rat) and 540X (monkey) the systemic exposure observed in humans at the recommended clinical dose of 2 mg (AUC_{0-t} of 999.9 ng•day/mL or 23.99 µg•hr/mL). Therefore, it is considered unlikely that systemic tissue vacuolization and other adverse effects identified in the 7-day continuous IV dose studies will occur at the systemic exposures expected to be observed in humans at the intended dosing regimen.

Avacincaptad pegol was negative for genotoxicity based on a standard battery of studies including the bacterial reverse mutation assay, chromosomal aberration in mammalian cells and in vivo mouse bone marrow micronucleus assays.

The Applicant submitted a justification not to conduct carcinogenicity, fertility/early embryonic development, and pre-/postnatal development studies. The Pharmacology/Toxicology team concluded that the weight of evidence supports that the studies are not necessary for the intended dosing regimen and indication.

In the embryofetal development (EFD) toxicity studies in rats and rabbits, there was no avacincaptad pegol-related adverse effects on any measured maternal or fetal parameter at doses up to 1.2 mg/kg/day (NOAEL). In the rats, a dose-dependent increase in the incidence of a skeletal variation (short thoracolumbar supernumerary rib) was observed at all avacincaptad pegol dose levels. In the rabbits, there was an increased incidence of full thoracolumbar supernumerary ribs at the high dose. Supernumerary rib is one of the most common skeletal variants in rodent and rabbit

developmental toxicity studies. This abnormality was considered a non-adverse variation (would not be expected to affect long-term survival).

1.3 Recommendations

1.3.1 Approvability

The Pharmacology/Toxicology team recommends approval of Avacincaptad Pegol Solution for the proposed indication of treatment of geographic atrophy secondary to age-related macular degeneration. The nonclinical studies were adequate to inform risk.

1.3.3 Labeling

See Pharmacology/Toxicology team recommendations in a separate label review for this NDA.

2 Drug Information

2.1 Drug

CAS Registry Number: 1491144-00-3

Generic Name: Avacincaptad pegol sodium

Code Name: X01B, ARC1905, Zimura

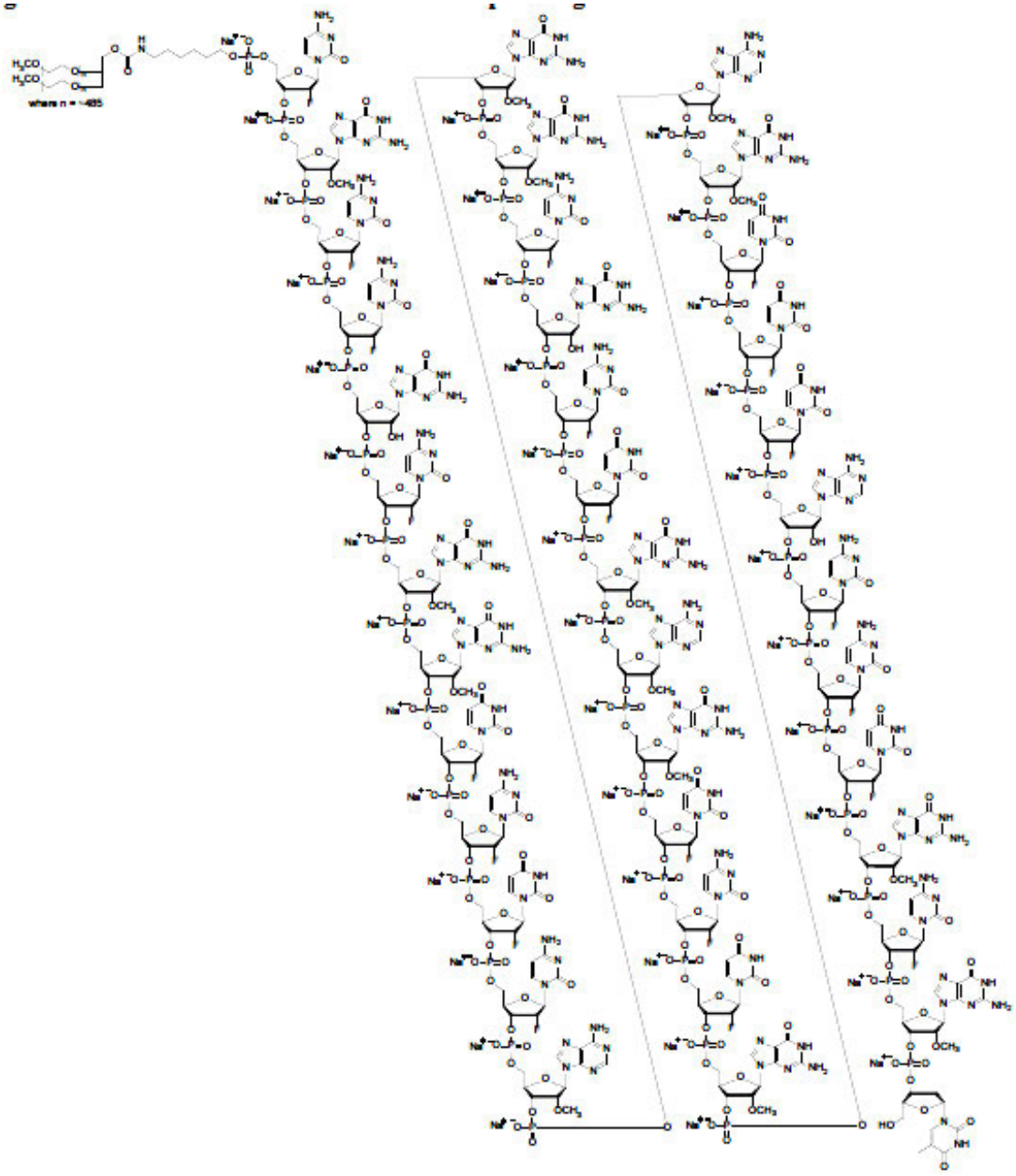
Chemical Name (IUPAC):

Poly(oxy-1,2-ethanediyl), α-hydro-ω-methoxy-, 5'-ether with RNA ((2'-deoxy-2'-fluoro)C-Gm-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)C-G-(2'-deoxy-2'-fluoro)C-Gm-Gm-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-Am-Gm-Gm-(2'-deoxy-2'-fluoro)C-G-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)U-Gm-Am-Gm-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)U-Gm-Am-Gm-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)U-A-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)U-Gm-(2'-deoxy-2'-fluoro)C-Gm-(3'→3')-dT) 5'-[6-[[(2,3-dihydroxypropoxy)carbonyl] amino]hexyl hydrogen phosphate], sodium salt (2:1:39).

Structure:

Avacincaptad pegol is a synthetically manufactured polyethylene glycol (PEG)-conjugated RNA aptamer that binds and inhibits complement component 5 (C5). It is composed of 39 oligonucleotides.

Figure 1: Chemical Structure of Avacincaptad Pegol Sodium



Source: Module 3.2.S.1.2

Molecular Formula:

Avacincaptad pegol is a PEGylated 39-mer oligonucleotide aptamer having the following sequence:

5'-[43 kDa PEG]-NH_2C_6-fC-mG-fC-fC-rG-fC-mG-mG-fU-fC-fU-fC-mA-mG-mG-fC-rG-fC-fU-mG-mA-mG-fU-fC-fU-mG-mA-mG-fU-fU-fU-rA-fC-fC-fU-mG-fC-mG-idT-3'

Legend:
rA, rG = *2'-ribonucleotides (Adenosine, Guanosine)*
fC, fU = *2'-fluoronucleotides (Cytidine, Uridine)*
mA, mG = *2'-O-Methyl nucleotides (Adenosine, Guanosine)*
idT = *inverted 2'-deoxyribonucleotide (Thymidine)*
NH_2C_6 = *Hexylamino Linker*
43 kDa PEG = *2,3-Bis(methylpolyoxyethylene-oxy)-1-yl propyl carbonate*

Length: 39mer + linker + PEG
Backbone: Phosphodiester

Non-PEGylated aptamer, free acid form: $C_{389}H_{482}N_{142}O_{258}P_{39}F_{21}$
Avacincaptad pegol, free acid form: $C_{395}H_{492}N_{142}O_{262}P_{39}F_{21}((CH_2)_2O)n$ where n~970

Molecular Weight:
Non-PEGylated avacincaptad pegol: 12,882 Da average mass (free acid form)
Avacincaptad pegol: 12,882 Da + ~43,000 Da PEG = ~55,882 Da

Pharmacologic Class: Complement component 5 (C5) inhibitor; complement inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 77902

2.3 Drug Formulation

The avacincaptad pegol drug product (DP) is a preservative-free, sterile, aqueous solution intended for single dose IVT administration. Drug product formulation is at a nominal concentration of 20 mg oligonucleotide per mL (20 mg/mL), (b) (4) (b) (4) and (b) (4) sodium chloride, at pH 7.3. The drug product is supplied with a fill volume of (b) (4) per vial. The composition of the drug product is shown in the Table 1.

Table 1: Composition of Avacincaptad Pegol Drug Product

Ingredient	Concentration (mg/mL)	Quantity (Per 0.1 mL Dose)	Quantity (Per Vial)[1]	Quality Standard	Function
Avacincaptad Pegol	20.0 (Oligonucleotide basis)[2]	2.0 mg (Oligonucleotide basis)	(b) (4)	In-house	Active ingredient
Dibasic Sodium Phosphate Heptahydrate	1.98	0.198 mg		USP	(b) (4)
Monobasic Sodium Phosphate Monohydrate	0.256	0.0256 mg		USP	
Sodium Chloride	8.3	0.83 mg		USP, Ph. Eur.	
Water for Injection	q.s.	q.s.		USP, Ph. Eur.	

[1] Quantity per vial (b) (4) mL) includes (b) (4) mL of excess fill to deliver 0.1 mL dose.
(b) (4)

q.s.: quantity sufficient

Source: Table 1, Module 3.2.P.1

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

The CMC review team requested feedback of the proposed impurity limits in the specification for the avacincaptad pegol drug substance.

For avacincaptad pegol, two different chromatographic methods are used for measuring levels of impurities in the drug substance:

1) Anion Exchange High Performance Liquid Chromatography (AX-HPLC)
2) Reversed Phase/Ion-Pair High Performance Liquid Chromatography (RP/IP-HPLC)

Both methods group impurities within ranges based on their Relative Retention Times (RRT) relative to the main peak (b) (4) due to the difficulty of resolving individual impurities of the PEGylated oligonucleotide.

For the Anion Exchange High Performance Liquid Chromatography (AX-HPLC) method, impurities are reported in two groupings from (b) (4), and from (b) (4) The proposed specifications are the following:

Impurities	AX-HPLC	Specified Impurities (b) (4) Unspecified Impurities (individual): (b) (4) Total Impurities (b) (4)

(b) (4)

Source: Excerpt from Table 1, Module 3.2.S.4.1

Per the Applicant's justification (Modules 3.2.S.4.5 Justification of Specification, pages 5 to 6), the toxicological batch (Lot X01B07001N) was retested using the current AX-HPLC method and the results for these impurities were summarized in Table 22 (copied below).

Table 22: Impurity level in DS of Toxicology Batch by AX-HPLC

Impurity	Toxicology Batch X01B07001N
(b) (4)	
Total	(b) (4)

The Applicant believes the nonclinical studies support the proposed specifications with the following justification:

- In IVT studies conducted on rabbits and dogs using lot X01B07001N, there were no significant findings from toxicity assessments which would indicate any risks for adverse reactions following exposure.
- In the chronic toxicology studies, dogs were dosed 3 mg (oligo)/eye with lot X01B07001N. The vitreous volume in a human eye is about twice the volume of the model dog eye. Therefore, the impurity levels qualified for human are (b) (4) of those in the toxicology studies.
- Total (b) (4) The level of this impurity band in Lot X01B07001N was (b) (4) Based on the discussion above, the impurity has been qualified at a level (b) (4) The impurity specification of (b) (4) has been set conservatively based on toxicology experience.
- Total (b) (4) The level of this impurity band was (b) (4). Based on the discussion above, the impurity has been qualified at a level (b) (4) of the toxicology level (b) (4) The impurity acceptance criterion of (b) (4) has been set conservatively based on toxicology experience.
- Total Impurities: From the toxicology study, the level of total impurities in Lot X01B07001N was (b) (4). Based on the discussion above, the impurity has been qualified at a level (b) (4) of the toxicology level (b) (4) Total impurities are mainly from components in the (b) (4)

and are potentially composed of [redacted]. The total impurity acceptance criterion of ≤ [redacted] has been set conservatively based on toxicology experience.

Reviewer's Conclusion - Impurities Qualified by AX-HPLC: *As noted in the tables below, the contents of each impurity at the NOAEL in the 9-month IVT toxicity studies in rabbits (1.5 mg/eye) and dogs (1 mg/eye) were higher than those calculated in humans at the proposed specifications (normalized by vitreous volume). The proposed specifications for the avacincaptad pegol drug substance impurities by AX-HPLC method are therefore qualified.*

Species	Levels evaluated of each impurity at the NOAEL	
	[redacted]	Total Impurities
Rabbit NOAEL: 1.5 mg/eye		[redacted]
Dog NOAEL: 1 mg/eye		

Note: Vitreous volumes of [redacted] in rabbits and [redacted] in dogs were used in the calculations.

Resulting impurity levels in humans at proposed specifications at the recommended dose of 2 mg are calculated as:

	[redacted]		
mg			
mg/mL vitreous			
Qualified	**Yes**	**Yes**	**Yes**

Note: Vitreous volume of 4 mL in humans was used in the calculations.

For the Reversed Phase/Ion-Pair High Performance Liquid Chromatography (RP/IP-HPLC) method, impurities are reported in a single grouping from [redacted] The proposed specifications are the following:

Impurities	RP/IP-HPLC	Specified Impurities	[redacted]
		Unspecified Impurities (individual):	
		Total Impurities	

Source: Excerpt from Table 1, Module 3.2.S.4.1

Initially, the Applicant did not provide adequate nonclinical data to qualify the proposed limits by RP/IP-HPLC method. An information request was sent to the Applicant to provide additional data to support the proposed specifications. In their response (SDN-15, received 4-12-2023), the Applicant clarified the drug substance

(batch # X01B07001N) used in the nonclinical toxicology studies was not analyzed by RP/IP-HPLC as the method was not available at the time of study conduct.

The Applicant clarified that the specified impurities (b) (4) detected by RP/IP-HPLC may also be impurities detected using AX-HPLC. Specified impurities (b) (4) detected by RP/IP-HPLC are high molecular weight PEG conjugates and these impurities may also be detected using AX-HPLC in the band of (b) (4)

Reviewer's comments: *In communications with the CMC review team, the team explained that the specified impurities detected by RP/IP-HPLC (b) (4) are present in samples analyzed using AX-HPLC and may be found in the (b) (4) (Full Length Product, i.e., drug substance) by AX-HPLC. In addition, some of these impurities may (b) (4) Since some of the impurities by RP/IP-HPLC are detected in the RRT range (b) (4) by AX-HPLC, and the rest may (b) (4)*

The Applicant explained that they established their proposed RP/IP-HPLC specifications by calculating (b) (4)

The Applicant calculated qualified limits using the (b) (4) (Applicant Tables 3 and 4, copied below).

Table 3: Toxicology Qualified Impurity Limits with Batch X01B07001N by AX-HPLC Method

Impurities	Ratio of Toxicology Study Dose (3 mg) to Proposed Commercial Dose (2 mg)	Ratio of Vitreous Volume of Human Eye to That of Dog Eye	Total Ratio of Impurity Qualified for Human with Proposed Commercial Dose	%Impurities by AX-HPLC	Toxicology Qualified %Impurities Limits by AX-HPLC
					(b) (4)
Specified Impurities (b) (4) (b) (4)					
Total Impurities					

Table 4: Qualified Impurity Limits with Batch X01B07001N by RP/IP-HPLC Method

Impurities	RP/IP-HPLC and AX-HPLC Impurity Correlation Ratio	Toxicology Qualified %Impurities by AX-HPLC	Qualified %Impurities Limits by RP/IP-HPLC	Proposed Commercial Limit (%)
				(b) (4)
Specified Impurities (b) (4)				
Total Impurities				

Reviewer's Conclusion – Impurities Qualified by RP/IP/HPLC: *Because these calculations are estimates and are not based on actual measurements by this second method (i.e., RP-IP-HPLC) in the toxicology batch, the reviewer did not rely on this approach to make a safety assessment. As explained above, the specifications for AX-HPLC support those of RP/IP-HPLC* (b) (4) *and therefore, the proposed RP/IP-HPLC specifications are considered acceptable. The Applicant will continue evaluating these proposed limits as additional commercial experience is obtained.*

The CMC team also requested feedback on the following proposed impurity in the specifications for the avacincaptad pegol drug product.

Purity	AX-HPLC	(b) (4)
Impurities	AX-HPLC	Specified Impurities (b) (4)
		Unspecified Impurities (individual): (b) (4)
		Total Impurities (b) (4)

Source: Excerpt from Table 1, Module 3.2.P5.1

The resulting impurity levels in humans at the proposed specifications at the recommended dose of 2 mg are calculated as:

	(b) (4)	Total
mg		(b) (4)
mg/mL vitreous		
Qualified	**Yes**	**Yes** **Yes**

Note: Vitreous volume of (b) (4) in humans was used in the calculations.

Reviewer's Conclusion: *As noted in the table above, the resulting content in humans at the proposed specifications were within the contents of each impurity at the NOAEL in the 9-month IVT toxicity studies in rabbits (1.5 mg/eye) and dogs (1 mg/eye). The proposed specifications for the avacincaptad pegol drug product impurities by AX-HPLC method are therefore qualified.*

Unspecified Impurities:

The Applicant-proposed specifications for unspecified/unidentified impurities is (b) (4) for the drug product (AX-HPLC method), i.e., higher than the qualification threshold recommended in ICH Q3B (1.0% or 50 µg, whichever is lower). The Applicant justification was the following:

"Based on ICH Q3A and Q3B, at doses up to 2 g per day (note: actually, it is 2 mg per day), the qualification threshold for small molecule impurities is 0.10% (unidentified) or 1.0 mg daily intake (whichever is lower). Acceptance criterion of ≤ (b) (4) for unspecified/unidentified impurities (individual) is considered appropriate because of the following justifications:

(b) (4)

(b) (4)

Reviewer's Comments: *Pharm/Tox and CMC teams agreed that we cannot guarantee the unspecified/unidentified impurities can be of the non-concerning class (i.e.,* (b) (4) *There is no nonclinical data to support the safety of a specification of NMT* (b) (4)

Even though the applicant says that the dose can be administered up to 2 g/day, the actual MDD is 2 mg/day. In that case, the identification threshold is (b) (4) *and qualification threshold is* (b) (4) *Reducing the limits to* (b) (4) *would be appropriate. This is supported based on the identified levels observed by the RP/IP-HPLC method (* (b) (4) *for drug product in the clinical and registration lots), guidance recommendations, and is the same specification proposed for the drug substance. Pharm/Tox believed a specification of NMT* (b) (4) *was reasonable, and the request was made to the applicant. See CMC review for final decision on acceptable specifications.*

2.6 Proposed Clinical Population and Dosing Regimen

- Treatment of patients with GA secondary to AMD
- The recommended dose is 2 mg (0.1 mL of 20 mg/mL solution) administered by IVT injection once monthly (approximately every 28 ± 7 days)

2.7 Regulatory Background

- Pre-IND (Pre-IND 77902) meeting held on May 5, 2005; Meeting minutes dated June 2, 2005 (provided in the NDA, not found in DARRTS)
- General correspondence - Pre-IND 77902 – Nonclinical review filed in DARRTS on Sept 26, 2007
  - The Applicant provided a justification for species selection. Pharmacology/Toxicology team agreed that the rabbit and dog are acceptable species for ocular toxicity studies. See Section 4.4 Rationale for Species Selection of this review for more details.
- Initial IND (IND 77902) – Submitted May 29, 2008; Pharm/Tox review filed in DARRTS on Sept 26, 2008.
  - IND allowed to proceed.
  - The IND also included a justification for species selection. See Section 4.4 Rationale for Species Selection of this review for more details.

- Type C meeting - Nonclinical studies for NDA submission (SD # 88); Sponsor meeting held on Sept 8, 2021; Meeting minutes filed in DARRTS on Sept 21, 2021.
    - Nonclinical recommendations for (1) submission for a waiver request for FEED (fertility and early embryonic developmental) and PPND (pre- and postnatal developmental), along with the justification and supporting data, (2) conduct of embryofetal development studies in relevant species, and (3) submission of waiver request for carcinogenicity studies, along with a justification and supporting data.
    - The Agency recommended embryofetal development (EFD) studies in two relevant species be conducted to support the NDA. The Agency agreed that the Sponsor's proposal to use rabbit and rat models for the embryofetal development studies appeared reasonable, given limitations of other models.
- Pre-NDA briefing document (SD # 111) submitted April 4, 2022; Sponsor meeting held on May 27, 2022; Meeting minutes filed in DARRTS on June 16, 2022.
    - Pharmacology/Toxicology team agreed with overall table and contents for nonclinical information
- Submission request for Rolling review – Sept 7, 2022; Grant letter - Oct 7, 2022
- Type C Meeting (SD # 117) - Intermediate AMD indication - Sponsor meeting held on September 20, 2022; Meeting minutes filed in DARRTS on Sept 12, 2022.
    - Pharmacology/Toxicology team agreed that the nonclinical, clinical, and safety data available to date adequately support initiation of the proposed clinical study in patients with intermediate AMD. The Agency did not consider intermediate AMD to be a separate indication from GA.

3 Studies Submitted

3.1 Studies Reviewed

- Effect of ARC187 on the Pharmacodynamic Properties of Heparin and Protamine (Study No. C5-DI-001-05)
- Mouse Bone Marrow Erythrocyte Micronucleus Test with ARC1905 Given by Intravenous Injection (AC10VW.123. (b) (4)
- An Embryo-Fetal Development Study of Zimura Given by Intravenous Injection in Rabbits (20332454)
- An Embryo-Fetal Development Study of Zimura Given by Intravenous Injection in Rats (20334075)
- Request for Waiver of Carcinogenicity Studies
- Request for Waiver of Nonclinical Development and Reproductive Toxicity (DARRTS) Studies

3.1.1 Studies Previously Reviewed under the Initial IND

PHARMACOLOGY

- Affinity and Specificity of ARC1905 for Human C5 (C5-PHARM-001-05)
- ARC1905 Inhibition of Classical Complement Pathway Activation (C5-PHARM-002-05)
- ARC1905 Inhibition of Alternative Complement Pathway Activation (C5-PHARM-003-05)
- Off-Target Effects of ARC1905 *in vitro* on Coagulation and Complement Activation (C5-PHARM-006-05)
- Spectrum Screen Data Report (1059148)
- ARC1905 Inhibition of Complement Activation in a Tubing Loop Model of Cardiopulmonary Bypass Circulation (C5-PHARM-004-05)
- Anti-Complement Activity of ARC1905 Across Species: Human, Cynomolgus Monkey, and Rat (C5-PHARM-005-05)
- A Single-Dose Range-Finding Study in Cynomolgus Monkeys of the Toxicity, Toxicokinetics, Pharmacodynamics and Toxicodynamics of ARC1905 Administered Intravenously by Bolus Injection Followed by Continuous Infusion Over 24 Hours Once with a 14-Day Recovery Period (KSH00033)
- A Repeated-Dose Study in Cynomolgus Monkeys of the Toxicity, Toxicokinetics, Pharmacodynamics and Toxicodynamics of ARC1905 Administered Intravenously by Bolus Injection Followed by Continuous Infusion for 7 Consecutive Days with a 1- or 14-Day Recovery Period (KSH00040)

SAFETY PHARMACOLOGY

- Effect of ARC1905 on Cloned hERG Channels Expressed in Mammalian Cells (050601)
- A Cardiovascular and Respiratory Safety Pharmacology Study of RAC1905 Administered Intravenously to Cynomolgus Monkeys (KSH00039)
- A Central Nervous System (CNS) Safety Pharmacology Study of ARC1905 Administered by Bolus Intravenous Injection to Sprague-Dawley Rats (KSH00043)

PHARMACOKINETICS

Absorption

- Pharmacokinetics and Bioequivalence of ARC187 (b) (4) 40 kDa PEG) and ARC1905 (b) (4) 40 kDa PEG) after IV Administration to Female CD-1 Mice (C5-PK-001-05)
- Pharmacokinetic Aspects of ARC1905 and 17-[^{33}P] -ARC1905 After Intravenous Bolus Administration to Male Sprague-Dawley Rats (C5-PK-002-05)

Distribution

- A Pharmacokinetic Study of Arch1905 Administered as an Intravitreal Bolus Dose in Dutch-Belted Rabbits (C5-PK-001-07)
- ARC1905 Plasma Protein Binding (KSH00061)

Metabolism

- Stability of ARC1905 in Human, Rat, and Cynomolgus Monkey Serum (C5-MS-001-05)
- Stability of ARC1905 in a Human Liver Microsomal Preparation (KSH00057)
- Metabolic Stability of ARC1905 in Human, Cynomolgus Monkey, and Rat Liver S9 Fractions (KSH00065)
- Effect of ARC1905 on Human Recombinant Cytochrome P450 Enzyme Activity (KSH00058)

Elimination

- Preliminary Mass Balance of Anti-C5 Aptamer 17-[^{33}P]-ARC1905 Following IV Administration to Male Sprague-Dawley Rats at 10 mg/kg (C5-BD-002-05)

Toxicokinetics

- A 1-Month (Single-Dose) and 9-Month (Ten-Dose) Toxicity Study of ARC1905 Given by Intravitreal Injections to Rabbits with and Without Combination Treatment with Lucentis™ (XGL00005)
- A 1-Month (Single-Dose) and 9-Month (Ten-Dose) Toxicity Study of ARC1905 Given by Intravitreal Injections to Beagle Dogs with and without Combination Treatment with Lucentis™ (XGL00006)
- Toxicokinetic Data from Study No. KSH00038, "A Single-Dose, Range-Finding Study in Sprague-Dawley Rats of the Toxicity, Toxicokinetics, and Toxicodynamics of ARC1905 Administered Intravenously by Bolus Injection Once with a 1-, 7-, or 14-Day Recovery Period" (C5-TK-002-05)
- Toxicokinetic Data from Study No. KSH00039, "A Cardiovascular and Respiratory Safety Pharmacology Study of ARC1905 Administered Intravenously to Conscious, Radiometry-Instrumented Cynomolgus Monkeys" (C5-SP-001-05)
- Toxicokinetic Data from Study No. KSH00033, "A Single-dose Range-finding Study in Cynomolgus Monkeys of the Toxicity, Toxicokinetics, Pharmacodynamics and Toxicodynamics of ARC1905 Administered Intravenously by Bolus Injection followed by Continuous Infusion Over 24 hours Once with a 14-Day Recovery Period" (C5-TK-001-05)
- Toxicokinetic Data from Study No. 501280, "A Repeated-dose Study in Sprague-Dawley Rats of the Toxicity, Toxicokinetics and Toxicodynamics of ARC1905 Administered Intravenously by Bolus Injection followed by Continuous Infusion for 7 Consecutive Days with a 1- or 14-Day Recovery Period" (C5-TK-004-05)
- Toxicokinetic Data from Study KSH00040, "A Repeated-dose Study in Cynomolgus Monkeys of the Toxicity, Toxicokinetics, Pharmacodynamics and Toxicodynamics of ARC1905 Administered Intravenously by Bolus Injection followed by Continuous Infusion for 7 Consecutive Days with a 1- or 14-Day Recovery Period" (C5-TK-003-05)

REPEAT-DOSE SYSTEMIC TOXICITY STUDIES

- A Repeated-Dose Study in Sprague-Dawley Rats of the Toxicity, Toxicokinetics and Pharmacodynamics of ARC1905 Administered Intravenously by Bolus

Injection followed by Continuous Infusion for 7 Consecutive Days with a 1- or 14-Day Recovery Period (501280)
- A Repeated-Dose Study in Cynomolgus Monkeys of the Toxicity, Toxicokinetics, Pharmacodynamics, and Toxicodynamics of ARC1905 Administered Intravenously by Bolus Injection followed by Continuous Infusion for 7 Consecutive Days with a 1- or 14-Day Recovery Period (KSH00040)

OCULAR TOXICITY STUDIES
- 1-Month (Single-Dose) and 9-Month (Ten-Dose) Toxicity Study of ARC1905 Given by Intravitreal Injections to Rabbits with and without Combination Treatment with Lucentis™ (XGL00005)
- A 1-Month (Single-Dose) and 9-Month (Ten-Dose) Toxicity Study of ARC1905 Given by Intravitreal Injections to Beagle Dogs with and without Combination Treatment with Lucentis™ (XGL00006)

GENOTOXICITY
- Bacterial Reverse Mutation Assay of ACRC1905 (AB12SY.503 (b) (4))
- *In Vitro* Mammalian Chromosome Aberration Test of ACR1905 (AB12SY.341. (b) (4))

3.1.2 Studies Previously Reviewed under SDN-16

- A 1-Month (Single-Dose) and 9-Month (Ten-Dose) Toxicity Study of ARC1905 Given by Intravitreal Injections to Rabbits with and without Combination Treatment with Lucentis (XGL00005)
- A 1-Month (Single-Dose) and 9-Month (Ten-Dose) Toxicity Study of ARC1905 Given by Intravitreal Injections to Beagle Dogs with and without Combination Treatment with Lucentis (XGL00006)

3.2 Studies Not Reviewed

- A Tolerability Study of Zimura by Intravenous Injection in Pregnant Rabbits (20332453)
- A Tolerability Study of Zimura by Intravenous Injection in Pregnant Sprague (20334072)

3.3 Previous Reviews Referenced

- Pre-IND 77902 review; Chen, filed in DARRTS on 9-26-2007
- Initial IND 77902 review; Chen & Rivera, filed in DARRTS on 9-26-2008
- IND 77902 SDN16 review; Rivera, filed in DARRTS on 10-13-2015

4 Pharmacology

4.1 Primary Pharmacology

Avacincaptad pegol (also referred to as ARC1905 or Zimura) is a polyethylene glycol (PEG)-conjugated ribonucleic acid (RNA) aptamer, which binds to human C5 component of human complement (C') with high affinity and specificity and inhibits complement activation. ARC1905 inhibits the conversion of C5 to C5a, a potent anaphylatoxin and chemotaxin, and C5b, which joins with C6 through C9 to form the lytic membrane attack complex, C5b-9.

The pharmacological effect of avacincaptad pegol is mediated by the binding and inhibition of C5 activation, thereby preventing the formation of key terminal fragments (C5a and C5b-9), which are considered to have an important role in the pathophysiology of GA. Therefore, inhibition of C5 may potentially slow down the progression of the disease.

A comprehensive series of nonclinical pharmacology studies was conducted to characterize the mechanism of action, primary and secondary pharmacologic effects, and safety pharmacology profile of avacincaptad pegol. These studies were previously reviewed under the initial IND (Chen & Rivera, filed in DARRTS on 9-26-2008). The key findings of these studies are listed in the following bullets and table.

All concentrations and doses for avacincaptad pegol are based on the mass of the oligonucleotide portion, exclusive of the PEG mass, unless stated otherwise.

- ARC186 (the core nucleic acid moiety of ARC1905) bound to human C5 with high affinity (K_D = 0.14 ± 0.036 nM at 25^{o}C and 0.41 nM ± 0.056 at 37^{o}C, 1.8 ng/mL and 5.3 ng/mL, respectively) and high specificity.
- 5'-modification of ARC186 with PEG (ARC1905) had no effect on the observed affinity (K_D at 25°C = 0.15 ± 0.048 nM [1.9 ng/mL]; K_D at 37°C = 0.69 ± 0.148 nM [8.9 ng/mL]).
- In competition binding assays, the aptamer also recognizes C5b,6 and C5b-9, although with approximately 10- and 1000-fold lesser affinity (K_D ≈ 6.5 nM [83.7 ng/mL] and ≥ 300 nM [3.9 µg/mL], respectively). The aptamer does not recognize C1q, C3, C4, C5a des Arg, C6 or the complement regulatory proteins, Factor B and Factor H.
- In a sheep erythrocyte hemolysis assay, the classical pathway of human complement activation was inhibited by ARC1905 with an IC_{50} value of 0.6 nM (7.7 ng/mL) and IC_{99} value of 5.09 nM (65.6 ng/mL). ARC1905 inhibited activation of monkey complements with an IC_{50} value of 3.65 nM (47 ng/mL).
- In an in vitro assay using zymosan to activate the alternative complement pathway, ARC1905 inhibited C5 activation (measured by generation of C5a) in both human (IC_{50} = 196 nM [2.5 µg/mL]) and monkey (IC_{50} = 536 nM [6.9 µg/mL]) sera. ARC1905 at concentrations of up to 2 µM (25.8 µg/mL) did not inhibit C3a

generation, indicating that upstream complement activation was not negatively impacted by ARC1905.

- Evaluation of anti-complement activity across species using a sheep erythrocyte hemolysis assay, the IC_{50} values were 0.35 ± 0.90 nM (4.5 ng/mL) for human serum, 3.69 ± 0.60 nM (47.5 ng/mL) for cynomolgus monkey serum, and 2700 ± 470 nM (34.8 µg/mL) for rat serum. Substantial (up to ~80%) inhibition was observed against rat complement activation at high concentrations of avacincaptad pegol (1 to 10 µM; 12.9 to 129 µg/mL).

Table 2: Main Findings of In Vitro Primary Pharmacology Studies

Type of Study/Description	Test System	Method of Administration	Dose	Gender, No. per Group	Noteworthy Findings	Study Report/ Number (Location)
Affinity and specificity of avacincaptad pegol for human C5	Isolated human proteins	*In vitro*	NA	NA	- High affinity and specificity for human C5. (C1q, C3, C4, C5a des Arg, C6 or C' regulatory proteins, Factor B and Factor H not recognized).	C5-PHARM-001-05 (M.4.2.1.1)
Avacincaptad pegol inhibition of classical complement pathway activation	Sheep erythrocyte hemolysis assay in presence of human and cynomolgus monkey complement components	*In vitro*	NA	NA	- Complete (90-99%) *in vitro* inhibition of complement activity achieved in human and monkey sera (effects approximately 10-fold less potent in monkey model).	C5-PHARM-002-05 (M.4.2.1.1)
Avacincaptad pegol inhibition of alternative complement pathway activation	Human and cynomolgus monkey sera	*In vitro*	NA	NA	- Essentially complete *in vitro* blockade of C5 activation in both species. - Upstream complement activation was not affected. - C3a generation was not inhibited up to 2 µM avacincaptad pegol concentration.	C5-PHARM-003-05 (M.4.2.1.1)

Type of Study/Description	Test System	Method of Administration	Dose	Gender, No. per Group	Noteworthy Findings	Study Report/ Number (Location)
Avacincaptad pegol inhibition of complement activation in a tubing loop model of cardiopulmonary bypass circulation	Cardiopulmonary bypass model	*In vitro*	NA	NA	- Inhibition of C5a generation, but not C3a.	C5-PHARM-004-05 (M.4.2.1.1)
Anti-complement activity of avacincaptad pegol across species: human, cynomolgus monkey, and rat	Sheep erythrocyte hemolysis assay in presence of human, cynomolgus monkey or rat complement components	*In vitro*	NA	NA	- Complete (90-99%) inhibition *in vitro* of complement activity in human and cynomolgus monkey sera (but approximately 10-fold less potent against monkey complement vs. human). - Little to no specific inhibitory activity observed against rat complement activation at low concentrations, but inhibition was observed at high [1-10 µM] concentrations.	C5-PHARM-005-05 (M.4.2.1.1)
Qualification of chicken and sheep erythrocyte hemolysis assays	Chicken and sheep erythrocyte hemolysis assay in presence of normal human serum	*In vitro*	NA	NA	- Pharmacodynamic assays evaluated for use in monitoring avacincaptad pegol anti-C5 activity in clinical trial subjects.	C5-PHARM-008-05 (M.4.2.1.1)
Type of Study/Description	**Test System**	**Method of Administration**	**Dose**	**Gender, No. per Group**	**Noteworthy Findings**	**Study Report/ Number (Location)**
					- Chicken erythrocyte hemolysis assay: Inter- and intra-assay reproducibility was confirmed. Analysis of individual samples should be performed with a range of serum dilutions to obtain a CH50. - Sheep erythrocyte hemolysis assay: sufficiently reproducible across donors and acceptable for testing complement activity in a single dilution of patient serum.	

Primary pharmacodynamics (PD) activity, in the context of C5 inhibition, was investigated in vivo in the cardiovascular and respiratory safety pharmacology study, single-dose toxicity study, and repeat-dose toxicity study in monkeys. These studies were reviewed in the initial IND (Chen & Rivera, filed in DARRTS on 9-26-2008) and key findings are summarized in Table 3.

Blood samples were collected for evaluation of PD parameters: ex vivo inhibition of classical complement pathway-mediated hemolysis of antibody-coated sheep red blood cells (sRBC) (referred to as measuring the animal total complement function [ATCF]) and ex-vivo inhibition of zymosan-mediated alternative complement pathway

activation to generate C5a. The studies and key findings are summarized in Table 3 below. The doses are based on oligonucleotide mass, excluding the mass of PEG.

Table 3: In Vivo Inhibition of Complement C5 Activity

Type of Study/Description	Test System	Method of Administration	Dose	Gender, No. per Group	Noteworthy Findings	Study Report/ Number (Location)
Cardiovascular and respiratory safety pharmacology in conscious, radiometry-instrumented cynomolgus monkeys	Cynomolgus monkeys (adult)	Intravenous (bolus)	0, 10, 30 and 100 mg/kg	1M	- At 0.5 and 2 hours after dosing avacincaptad pegol at ≥ 10 mg/kg was associated with > 95% inhibition of ATCF and 69% to 78% inhibition of zymosan-mediated generation of C5a.	KSH00039 (M.4.2.1.3)
Single-dose range-finding study and toxicity, toxicokinetics, pharmacodynamics and toxicodynamics of avacincaptad pegol in cynomolgus monkeys	Cynomolgus monkeys	Intravenous by bolus injection followed by continuous infusion over 24 hours once	IV bolus: 0, 1, 3, 10, 30 and 100 mg/kg Continuous IV infusion: 0, 2.9, 8.6, 28.7, 86.2 or 287 mg/kg	1M, 1F	- ≥ 98% inhibition of ATCF was attained only at doses ≥ 28.7 mg/kg and was maintained during the 24-hour infusion. - Maximal inhibition of complement activity observed with the sheep erythrocyte hemolysis assay was 81% at the highest dose of 287 mg/kg and a dose-dependent effect was evident.	KSH00033 (M.4.2.3.1)
Repeated-dose study and toxicity, toxicokinetics, pharmacodynamics and toxicodynamics of avacincaptad pegol in cynomolgus monkeys	Cynomolgus monkeys	Intravenous by bolus injection followed by continuous infusion for 7 consecutive days	IV bolus: 0, 10, 30, 100 mg/kg Continuous IV infusion: 0, 141, 423, 1410 mg/kg	3-5M, 3-5F	- Avacincaptad pegol at ≥ 141 mg/kg was associated with dose-dependent inhibition of complement activity, as indicated by decreases in ATCF values, post-zymosan C5a concentrations and sRBC and cRBC hemolysis.	KSH00040 (M.4.2.3.2)

ATCF = animal total complement function; C5 = complement component 5; CH50 = C4, hemolytic complement 50; cRBC = chicken red blood cell; F = female; IV= = intravenous; M = male; NA=not applicable; sRBC = sheep red blood cell

In all these studies, the relationship of plasma ARC1905 concentration to complement inhibition was also determined. Key findings include:

- In cardiovascular and respiratory safety pharmacology studies in monkeys (Study No. KSH00039), all doses of avacincaptad pegol (mean concentrations ≥ 154 µg/mL) were consistently associated with > 95% inhibition of animal total complement function (ATCF) regardless of dose or timepoint (Table 4)

Table 4: Relationship of Plasma ARC1905 Concentrations to Inhibition of C' Activity (Study No. KSH00039)

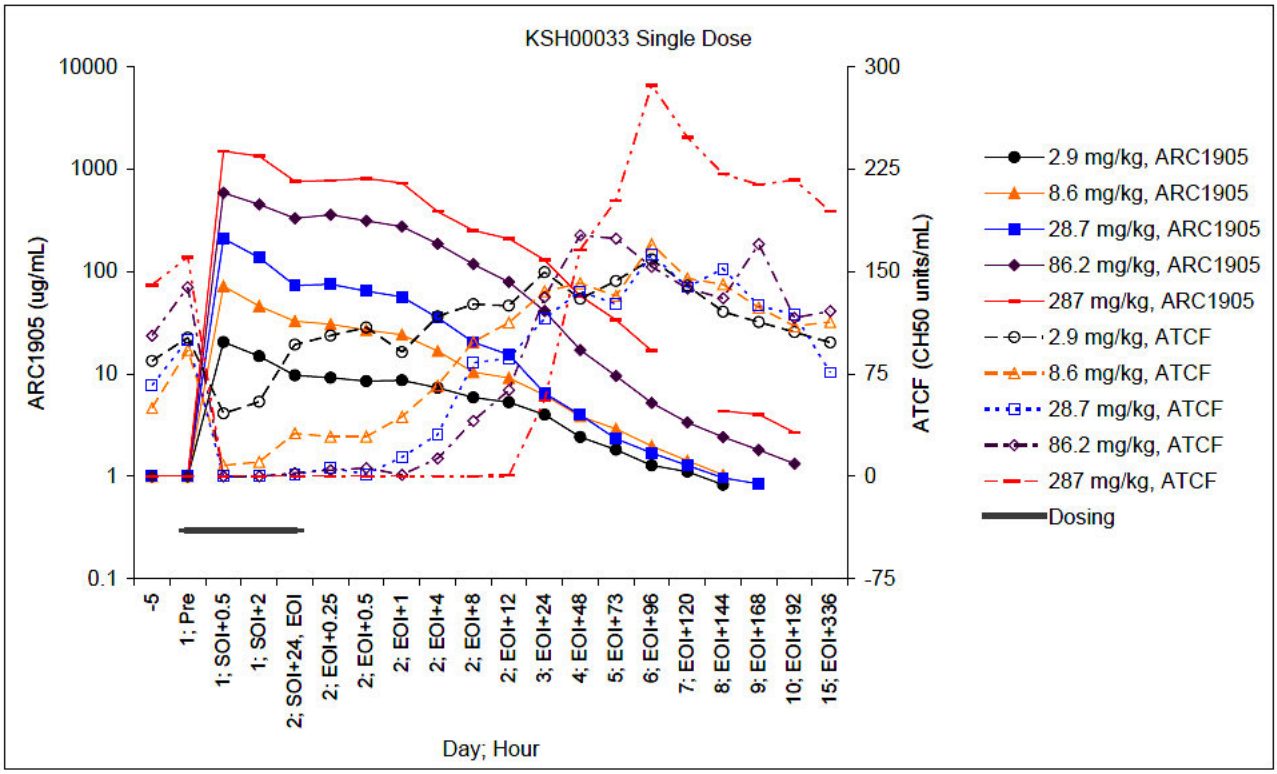
KSH00039 Relationship of Plasma ARC1905 Concentrations to Inhibition of C' Activity

Dose (mg/kg)	Day; Hour	Plasma ARC1905 (µg/mL)	Inhibition of ATCF (%)
NA	-5	< LLOQ	
0 mg/kg	1; Pre	< LLOQ	0%
	1; 0.5	< LLOQ	8%
	1; 2	< LLOQ	7%
	2; 24	< LLOQ	
10 mg/kg	8; Pre	< LLOQ	0%
	8; 0.5	220	97%
	8; 2	154	95%
	9; 24	14	
30 mg/kg	22; Pre	< LLOQ	0%
	22; 0.5	701	100%
	22; 2	508	100%
	23; 24	35	
100 mg/kg	36; Pre	< LLOQ	0%
	36; 0.5	2072	100%
	36; 2	1595	100%
	37; 24	140	

LLOQ = lower limit of quantitation = 0.820 µg/mL; Pre = predose
Activity was not measured at 24 hours postdose.
Source: Study Report Table 8

- In the single-dose range-finding study in monkeys (Study No. KSH00033), all doses of avacincaptad pegol evaluated (≥2.9 mg/kg IV) were associated with dose-dependent inhibition of complement activity, as indicated by decreases in ATCF values (55 to 100% inhibition) and sRBC hemolysis (21 to 81%). At doses of 28.7, 86.2, and 287 mg/kg, mean plasma avacincaptad pegol concentrations were consistently > 130 µg/mL (the target pharmacological concentration in monkeys) through 2 hours after the start of infusion or 4 or 12 hours after the end of infusion, respectively. Avacincaptad pegol concentrations > 130 µg/mL were associated with ≥ 91% inhibition of complement activity (ATCF), regardless of dose or time point (Figure 2).

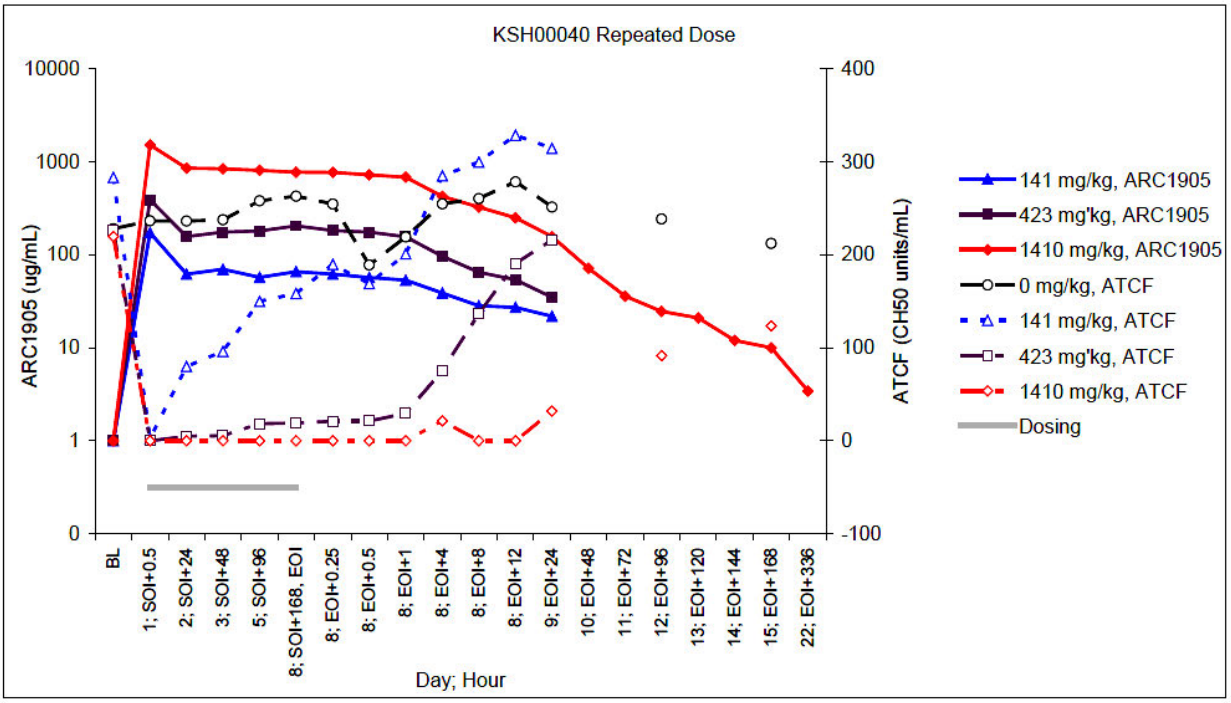
Figure 2: Relationship of Plasma Avacincaptad Pegol Concentrations to Inhibition of Complement Activity (ATCF) after Single Intravenous Doses (Study No. KSH00033)



Source: Applicant's Figure 2.6.2.2-7, Pharmacology Written Summary

- In the 7-day repeat-dose study in monkeys (Study No. KSH00040), similar to the other studies, avacincaptad pegol concentrations > 130 µg/mL (actually ≥ 156 µg/mL), were associated with ≥ 86% inhibition of complement activity (ATCF), regardless of dose or timepoint (Figure 3). Inhibition of complement activity of < 86% was associated with mean avacincaptad pegol concentrations of ≤ 96 µg/mL. All doses of avacincaptad pegol evaluated (≥ 141 mg/kg IV) were associated with dose-dependent inhibition of complement activity, as indicated by decreases in ATCF values, post-zymosan C5a concentrations and sRBC and chicken RBC hemolysis. Results were generally similar among assays.

Figure 3: Relationship of Plasma Avacincaptad Pegol Concentrations to Inhibition of Complement Activity (ATCF) after Repeated Intravenous Doses



Source: Applicant's Figure 2.6.2.2-12, Pharmacology Written Summary

Reviewer's comments: *These in vivo studies in the monkey did not identify a non-pharmacologically active dose.*

4.2 Secondary Pharmacology

The affinity of avacincaptad pegol against a panel of rat and human proteins was evaluated using radioligand binding assays (Study No. 1059148). The study was reviewed under the initial IND (Chen & Rivera, filed in DARRTS on 9-26-2008).

ARC1905 partially inhibited radioligand binding for 13 of approximately 160 proteins (Table 5) of which 8 were of human origin and 5 were of rat origin (Study No. 1059148). Approximate IC_{50} values for the human proteins ranged from 0.268 to 10.6 µM (3.45 to 137.8 µg/mL, based on oligonucleotide content).

The IC_{50} values were higher than the mean plasma concentrations of avacincaptad pegol measured following IVT injection in the rabbit and dog chronic ocular toxicity studies (≤51.3 ng/mL in rabbits; ≤488.7 ng/mL in dogs) or humans (68.4 ng/mL). The IC_{50} values are ≥50X higher than human plasma concentrations. The data support that no significant in vivo interaction is expected between avacincaptad pegol and the 13 proteins listed in Table 5.

Table 5: Avacincaptad Pegol Protein Specificity Screening

Biochemical Assay	Species	Conc. (µM)	% Inhibition	IC_{50} (µM)	K_I (µM)	n_H
Neuromedin U NMU2	Human	1	84	0.268	0.177	1.15
Chemokine CCR4	Human	1	62	0.419	0.220	0.729
Colchicine	Rat	1	75	0.344	0.343	1.08
Calcium Channel N-Type	Rat	3	74	1.11	0.929	1.18
Potassium Channel [KA]	Rat	3	57	1.63	1.27	1
Tumor Necrosis Factor (TNF), Non-Selective	Human	3	64	1.84	1.32	1.47
Vasoactive Intestinal Peptide VIP1	Human	3	53	2.25	1.58	1.4
Glycine, Strychnine-Sensitive	Rat	3	52	4.16	2.35	0.533
Epidermal Growth Factor (EGF)	Human	10	57	6.04	2.36	0.597
Galanin GAL1	Human	10	69	5.61	3.63	1.21
Chemokine CXCR2 (IL-8B)	Human	10	51	10.3	7.20	1.14
Adrenergic α1A	Rat	10	57	20.0	8.11	0.844
Corticotropin Releasing Factor CRF1	Human	10	55	10.6	9.57	1.05

Source: Applicant's Table 2.6.2.3-1, Pharmacology Written Summary

An in vitro assay using human plasma was conducted to evaluate off-target effects in coagulation, i.e., not related to C5 inhibition (Study No. C5-Pharm-006-05). The study was reviewed under the initial IND (Chen & Rivera, filed in DARRTS on 9-26-2008). The anticoagulant properties of ARC1905 were evaluated by clot time analysis, using the activated partial thromboplastin time (APTT) and the prothrombin time (PT) assays. The key findings included:

- ARC1905 prolonged APTT in a concentration-dependent manner with a 1.2-, 1.4- and 1.7-fold increase at 0.5, 1, and 2 mg/mL, respectively, with little or no effect on PT.
- These results indicate that avacincaptad pegol possesses mild anticoagulant properties at high concentrations.
    - The low plasma concentration observed in the clinical trials (mean C_{max} = 68.4 ng/mL) also supports low risk for anticoagulation effects in humans.

- Similar results were observed for ARC594 (a non-C5 specific aptamer of similar size and PEG content), suggesting that the observed effects on coagulation may be characteristic of aptamers in general.
- In the same study, ARC1905 did not induce complement activation (measured by C3a generation) in human serum at concentrations up to 2 mg/mL.

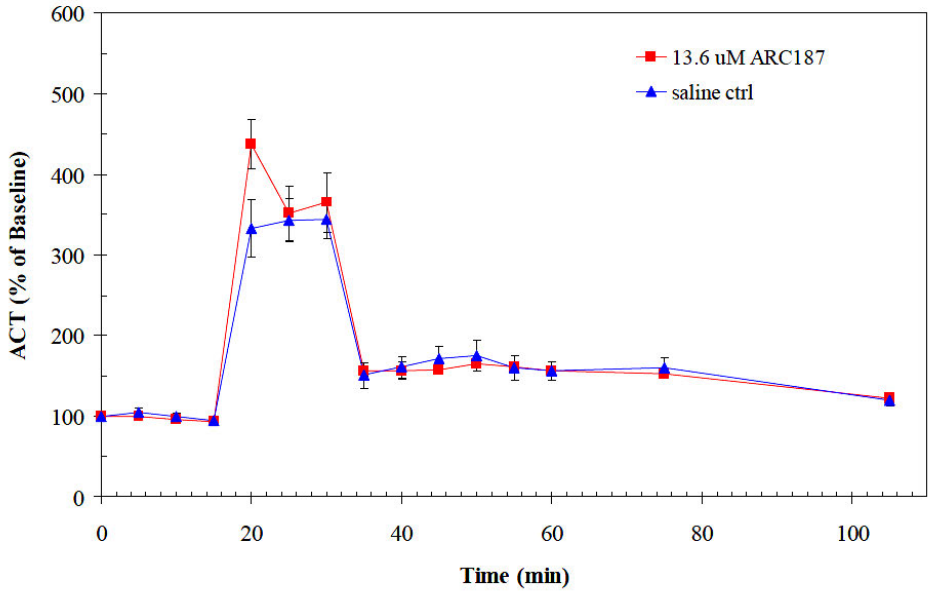
Increased APTT and/or PT values and/or decreased plasma fibrinogen levels were observed in several in vivo studies (addressed in other review sections below).

Effect of ARC187 on the Pharmacodynamic Properties of Heparin and Protamine (Study No. C5-DI-001-05) – ARC187 is a bioequivalent aptamer identical to avacincaptad pegol except for the source of 40 KDa PEG. ARC187 recognizes protamine and thrombin, although with approximately 360- and 7000-fold lesser affinity ($K_D \approx 150$ nM and 3000 nM, respectively) compared to that of C5 ($K_D \approx 0.42$ nM). This study was conducted to evaluate if, at a steady state, plasma concentration of 10 µM maintained by intravenous (IV) bolus followed by IV infusion, ARC187 can interfere with the pharmacologic effect of protamine to rapidly reverse the anticoagulant effects of heparin as measured by activated clotting time (ACT) versus a saline control.

Key Findings:

- IV bolus plus infusion administration of ARC187 (10.2 mg/kg, based on aptamer content, excluding the mass of PEG) in male Sprague-Dawley rats achieved the target concentration of ≥ 10 µM (equivalent to 128.9 µg/mL, based on oligonucleotide mass, excluding the mass of PEG) with a mean ARC187 concentration maintained at 13.60 µM.
- At plasma concentrations up to 13.60 µM, ARC187 did not interfere with the ability of heparin to serve as an anticoagulant during surgery or the ability of protamine to effectively reverse the effect of heparin in rats (Figure 4).

Figure 4: Mean ACT Values for Saline Control and ARC187 Groups



Source: Study Report Figure 10-6

4.3 Safety Pharmacology

These studies were previously reviewed under the initial IND (Chen & Rivera, filed in DARRTS on 9-26-2008).

A Central Nervous System (CNS) Safety Pharmacology Study of ARC1905 Administered by Bolus Intravenous Injection to Sprague-Dawley Rats (Study No. KSH00043) –Sprague-Dawley rats (6/sex/group) received single IV injection of ARC1905 at 0 (saline), 26, 100 or 260 mg/kg. The rats were evaluated for CNS effects (including behavior, autonomic functions, appearance, locomotor activity, gait, auditory reaction, and other parameters), body temperature, body weight and clinical observations on Day 1 at 15 to 30 min after dosing, and on Day 2 at 24 hours after dosing.

Key findings:

- There were no ARC1905-related clinical observations or neurologic abnormalities at doses up to 260 mg/kg.
- The NOAEL in this study was 260 mg/kg.

Effect of ARC1905 on Cloned hERG Channels Expressed in Mammalian Cells (Study No. 050601) - Relative to baseline (negative control) values, ARC1905 mean percent inhibition (± standard error of the mean) was 0.8 ± 0.5% (n=3) at 10 µM and

10.1 ± 1.3% (n=5) at 100 µM. The IC_{50} was not determined but considered to be > 100 µM, supporting minimal risk for QTc prolongation.

A Cardiovascular and Respiratory Safety Pharmacology Study of Avacincaptad Pegol Administered Intravenously to Conscious, Radiometry-Instrumented Cynomolgus Monkeys (Study No. KSH00039) - Four male monkeys were implanted with a radiotelemetry transmitter. All animals received IV bolus injections of 0 (saline), 10, 30, and 100 mg/kg ARC1905 on Days 1, 8, 22, and 36, respectively. Cardiovascular and respiratory parameters including mean blood pressure (MAP), heart rate (HR), body temperature, ECG (qualitative features as well as quantitative assessment of RR, QT and QTc intervals), partial pressures of CO_2 and O_2, pH, percentage saturation of hemoglobin with oxygen (SaO_2), and respiratory rate were monitored.

Key findings:

- As noted above, ARC1905 prevented activation of the classical and alternative complement pathways. At 0.5- and 2-hour postdose, the drug at ≥ 10 mg/kg was associated with dose-dependent inhibition of animal total complement function (ATFC, 97-100% inhibition) and zymosan-mediated generation of C5a (77 to 69% inhibition).
- ARC1905 was associated with mildly increased mean PT values (19%) at 0.5 hour after dosing at 100 mg/kg, and moderately increased mean APTT values (76 and 80%) 0.5-hour postdose at ≥ 30 mg/kg (Table 6).
    - *Per information in the Study Report: "Antisense oligonucleotide compounds have been reported to have non-specific anticoagulant properties in cynomolgus monkeys, attributable to inhibition of the intrinsic coagulation pathway (ref provided). Inhibition of the tenase complex (consisting of Factor IXa, Factor VIIIa, phospholipids and calcium) occurs at plasma oligonucleotide concentrations < 100 µg/mL and inhibition of thrombin at concentrations > 100 µg/mL. This toxicodynamic effect results in elevations to APTT values."*
    - *Study Report No. C5-Pharm-006-05 (see above), supports that the anticoagulant activity is unrelated to C5 inhibition.*

Table 6: Effects on Coagulation Parameters – Cardiovascular and Respiratory Safety Pharmacology Study in Monkeys (Study No. KSH00039)

KSH00039 Coagulation Profile Results										
		Mean			SD			% Change from Baseline		
Dose (mg/kg)	Day; Hour	APTT (sec)	PT (sec)	Fib (mg/dL)	APTT (sec)	PT (sec)	Fib (mg/dL)	APTT (sec)	PT (sec)	Fib (mg/dL)
Baseline	-5	24.4	11.0	232	2.0	0.3	14	NA	NA	NA
0	1; 0.5	24.9	11.1	192	2.0	0.4	6	2%	1%	-17%
	2; 24	24.2	10.8	210	2.2	0.3	16	1%	-2%	-9%
10	8; 0.5	26.7	11.0	190	2.6	0.4	11	9%	0%	-18%
	9; 24	23.9	10.5	218	1.9	0.4	16	-2%	-5%	-6%
30	22; 0.5	42.9	17.4	155	21.1	11.9	16	76%	58%	-33%
	23; 24	24.3	11.0	201	2.2	0.6	40	0%	0%	-13%
100	36; 0.5	43.8	13.1	127	7.2	0.6	12	80%	19%	-45%
	37; 24	29.1	12.2	218	2.7	0.4	38	19%	11%	-6%

NA = not applicable

Source: Study Report Table 3 (not included in the initial IND review)

- *ARC1905 at 30 and 100 mg/kg was associated with a dose-dependent, moderate (33% and 45%, respectively) decrease in mean plasma fibrinogen concentrations at 0.5 hours after dosing. At 0 and 10 mg/kg, fibrinogen values were mildly (17% and 18%) decreased at 0.5 hours after dosing, suggesting a procedure-related contribution to the finding.*
- IV doses of ARC1905 up to 100 mg/kg had no effects on cardiovascular and respiratory parameters or body temperature.
- Summary TK data is shown in the Table below.

Table 7: Toxicokinetic Parameter Estimates After Single IV Bolus Administration of ARC1905 in Male Cynomolgus Monkeys

KSH00039 TK Parameter Estimates							
Toxicokinetics Parameters Estimates	Dose (mg/kg):	10		30		100	
	Unit	Mean	SD	Mean	SD	Mean	SD
T_{max}	hr	0.5	0.00	0.5	0.00	0.5	0.00
C_{max}	µg/mL	220	13.4	701	22.2	2072	198.1
NC_{max}	kg·µg/mL·mg	22	1.3	23	0.7	21	2.0
$AUC_{0\text{-last}}$	µg·hr/mL	2238	113.9	7255	333.2	22927	1297.8
$NAUC_{0\text{-last}}$	kg·µg·hr/mL·mg	224	11	242	11	229	13
$MRT_{0\text{-last}}$	hr	3.3	0.39	3.0	0.35	3.3	0.80

Source: Study Report Table 10 (not included in the initial IND review)

- The NOAEL for cardiovascular and respiratory findings in this study was the high dose, 100 mg/kg. The C_{max} is over 30000X higher than the mean plasma exposure observed at the recommended clinical dose (68.4 ng/mL).
- The C_{max} at the NOEL of 10 mg/kg for the increased in APTT values is 3216X higher than the mean plasma exposure observed at the recommended clinical dose (≤68.4 ng/mL).

4.4 Rationale for Species Selection

The monkey is the only species identified that could be considered relevant showing 1/10th of the ARC1905 in an *in vitro* activity assay against human C5. The rat has 1/1000th of the in vitro activity against human C5. The ocular studies were conducted in rabbit and dogs, which, as the Applicant indicated, are species in which ARC1905 is expected to have very low activity. Experience with clinical administration of a systemic C5 inhibitor identified an increase susceptibility to infections as the main adverse effect related to the pharmacology of the drug. After consideration of the clinical experience and the factors listed below, the Division decided not to ask for ocular toxicity studies in monkeys unless unexpected findings in the clinical studies warranted further investigation in these species.

The Applicant's justifications for accepting the rabbit and dog in the ocular toxicity studies were reviewed at the Pre-IND and Initial IND stages (see Pre-IND review, Chen, filed in DARRTS on 9-26-2007, and IND 77902 initial nonclinical review, Chen & Rivera, filed in DARRTS on 9-26-2008). Excerpts from the initial IND review are listed below (unless otherwise specified). Note that the reviewer comments below are also from these initial reviews (they are not current NDA comments).

- There are no animal species in which the human anti-C5 aptamer can be tested in ocular toxicity studies for effects stemming from C5 binding.

    - *Reviewers' comment: As stated above, monkeys showed 1/10th of the activity, rodents showed 1/1000th, and activity in other non-primate species is expected to be low.*

- Systemic toxicity studies in monkeys with large IV doses (high enough to achieve adequate exposure to potentially elicit a pharmacological response due to C5 binding) showed no adverse events related to the C5 inhibition.

    - *Reviewers' comment: There were some findings that were common to both rats and monkeys including the macrophage vacuolation in multiple tissues and prolonged APTT and PT, and not unexpected based on experience with the antisense oligonucleotide class or other PEGylated molecules. The mechanism for the bone marrow suppression and rouleaux formation is not clear, but these findings were probably unrelated to C5 inhibition.*

- Inhibition of C5 activity appears to have no unexpected safety issues.

    - *Reviewers' comment: In regard to the safety profile of C5 inhibition, the main adverse effect reported for Soliris® (eculizumab), a humanized monoclonal antibody against C5 approved on March 16, 2007 for systemic use (600 mg IV every 7 days followed by 900 mg 7 days later and 900 mg every 14 days thereafter) in patients with paroxysmal nocturnal hemoglubinuria to reduce hemolysis, is an increased risk for serious meningococcal infections. Other common adverse effects (≥10% overall and greater than placebo) include headache, nasopharyngitis, back pain, and nausea. Therefore, it seems that the main adverse reaction due to an exaggerated pharmacological effect of complement inhibition is an increased susceptibility to infections.*

- The high doses in ocular studies will be limited by viscosity and inflammatory responses.

    - *Reviewers' comment: The maximum dose that can be administered is 1.5-3.0 mg/eye due to concentration and viscosity issues, doses that will provide a modest clinical multiple but will not be high enough to produce exaggerated pharmacological activity.*

    - *Also, in the pre-IND review, the reviewer stated: However, because of the dosing limitations for ocular studies as mentioned earlier, the highest dose levels injected into the eye would not be sufficient to produce exaggerated pharmacologic activity in monkeys and other animal species. There is no animal species in which the human anti-C5 aptamer can be tested for C5*

binding-related effects in ocular studies. Therefore, the monkey has no advantage over the rabbit or dog, and the reviewer considers that the rabbit and dog are acceptable species.

4.5 Exposure Margin Correction for Species Differences in Pharmacological Activity

Based on in vitro data demonstrating 1/10th of the potency of avacincaptad pegol for cynomolgus monkey C5, the target concentration for avacincaptad pegol in cynomolgus monkey plasma after IV dosing was projected to be 10 µM (130 µg/mL). Based on this fact, it seems we can assume plasma concentrations of approximately 10 µg/mL will be required in humans for complete C5 inhibition. The clinical C_{max} was 68.3 ng/mL, over 140X lower than the estimated concentration for complete C5 inhibition.

For ocular toxicity findings, correction for species differences in pharmacological activity were not performed as the key findings (ocular tissue vacuolation, effects on APTT/PT) are unrelated to C5 inhibition.

Evaluations of anti-complement activity across species using a sheep erythrocyte hemolysis assay, substantial (up to ~80%) inhibition was observed against rat complement activation at high concentrations of avacincaptad pegol (1 to 10 µM; 12.9 to 129 µg/mL). The plasma concentrations in the rat EFD studies ranged from 2.64 to 25.7 µg/mL, which indicates significant target inhibition at least at the high dose. No data is available for the rabbit. However, exposure margins were not corrected for differences in pharmacological activity as high systemic target inhibition was expected at the high dose used (at least in rats) compared to minimal inhibition expected in humans at the observed clinical exposure (64.8 ng/mL, over 140X lower than the estimated concentration for complete C5 inhibition as noted above). In addition, the observed finding (increased incidence of thoracolumbar supernumerary ribs) is not considered adverse and likely of no clinical relevance.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

These studies were previously reviewed under the initial IND (Chen & Rivera, filed in DARRTS on 9-26-2008), except for Study No. KSH00062.

An ocular tissue distribution study was conducted in male Dutch-Belted rabbits following a single IVT injection of avacincaptad pegol (3 mg/eye) to both eyes (Study No. C5-PK-001-07). Plasma, vitreous, aqueous, and retinal tissue samples were collected at several timepoints up to 720 hours postdose. Samples were analyzed using both a dual hybridization pseudo-ELISA assay with a lower limit of quantitation (LLOQ) of 0.001 µg/mL, and an HPLC method with an LLOQ of 0.10 µg/mL.

The ARC1905 concentration-time profile was generally monophasic. ARC1905 parent compound was detected up to 720-hour (30 days) postdose in plasma and tissue samples. ARC1905 was detected in plasma via dual hybridization ELISA sample analysis (LLOQ 0.001 µg/mL); however, the concentration level was below the detection limit for the HPLC assay (LLOQ 0.1 µg/mL). Vitreous and aqueous samples (both eyes pooled), as well as retinal tissue samples were analyzed by both dual-hybridization ELISA and HPLC bioanalytical methods.

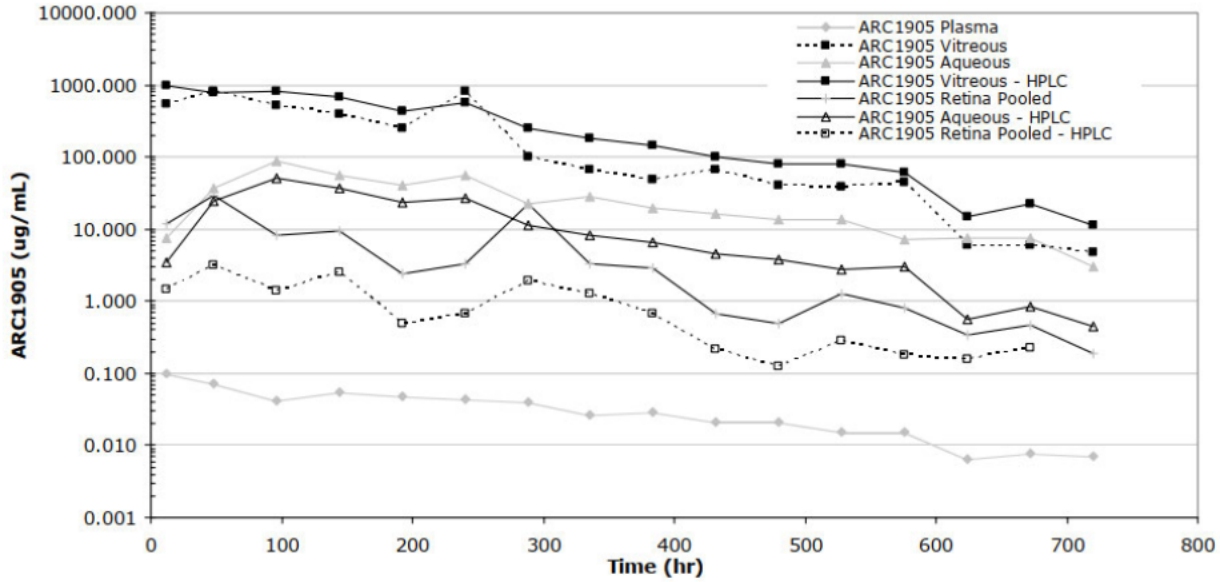
The HPLC assay method was shown to be capable of discriminating between full-length aptamer and chain-shortened metabolites (N-x, where x = 1-6), while the dual-hybridization ELISA was not. The fact that similar concentration values were derived for vitreous fluid using both analytical methods suggests that the concentrations measured using the dual-hybridization ELISA assay represent primarily full-length parent compound, even at the last sampling time of one-month postdose.

Avacincaptad pegol concentrations were substantially higher in the vitreous humor than in aqueous humor or retina, and it was clear that most of the injected aptamer remained in the vitreous compartment for an extended period (Table 8 and Figure 5). The avacincaptad pegol concentration in the vitreous humor 30 days postdose was 11.4 µg/mL (885 nM). The half-life ($t_{1/2}$) in the vitreous was 4 days (91.9 hours) and that in the plasma was 7.5 days (181.41 hours). From the vitreous humor, avacincaptad pegol migrated into other ocular structures, including the retina, and slowly egressed into the plasma, such that plasma kinetics were largely dictated by the migration out of the eyes.

Table 8: Mean PK Parameters of Avacincaptad Pegol following a Single IVT Bolus Administration to Male DB Rabbits at 3 mg/eye (Study C5-PK-001-07)

Parameter	Plasma	Vitreous	Aqueous	Retina - Pooled	Vitreous-HPLC	Aqueous - HPLC	Retina -Pooled -HPLC
C_{max} (µg/mL)	0.10	829.77	88.14	29.58	1,000.95	50.26	2.44
T_{max} (hr)	12.00	240.001	96.00	48.00	12.00	96.00	48.00
AUC_{last} (µg•hr/mL)	23.89	165,787.0 2	19,114.56	4,305.42	228,795.5 9	9,780.06	577.14
$t_{1/2}$ (β) (hr)	181.41	91.94	147.10	NC	102.62	93.50	NC

Figure 5: Mean Concentrations of Avacincaptad Pegol following Single IVT Bolus Administration to Male DB Rabbits at 3 mg/eye (Study C5-PK-001-07)



Source: Applicant's Figure 2.6.4.4-1, Pharmacokinetics Written Summary

The Applicant conducted several ADME studies in vitro and in vivo following IV administration. Based on the low systemic exposure observed after IVT injection, only some key findings are listed below. For further details, see the initial IND nonclinical review (Chen & Rivera, filed in DARRTS on 9-26-2008).

- After a single IV bolus administration, ARC1905 plasma $t_{1/2}$ was 5.6 hours (rats), 2.2 hours (mice) and 41 to 68.7 hours (monkey).
- In in vitro metabolic stability assays using serum samples, a potential metabolite constituted 9, 12, and 14% of the full-length parent peak at 24, 48, and 72 hours, respectively in cynomolgus serum. In rat serum, the potential metabolite peak constituted 0, 6, and 6% at 24, 48, and 72 hours, respectively. In human serum, the potential metabolite peak constituted 0, 6, and 6% at 24, 48, and 72 hours, respectively.
- ARC1905 was metabolically stable in vitro in human liver microsomes. In the presence of pooled human liver microsomes, no loss of avacincaptad pegol was observed at the 30-minute and 90-minute incubation timepoints (104% and 100% remaining, respectively).
- In the presence of human S9, the percentage of avacincaptad pegol remaining was 48% at 24 hours, with and without S9 replenishment (addition of S9 at 2 and 4 hours). The peak area for avacincaptad pegol ((b) (4) was significantly reduced, and multiple peaks were observed with both shorter (b) (4) and longer retention times. The identity of these product peaks is unknown.
- In contrast to the human S9 results, no ARC1905 test compound was detected (0% remaining) at the 6-hour timepoint in both cynomolgus monkey and rat S9 incubations, regardless of S9 replenishment. Many of these product peaks

appear to have approximately similar retention times as the human peaks. A small peak at approximately (b) (4) was observed in the 6-hour human and cynomolgus monkey samples, remained small in the human 24-hour sample, but was one of the major peaks (30%-50% by area) in the $T_{24hours}$ cynomolgus monkey and rat S9 samples.

- At 4 µM (51 µg/mL), ARC1905 inhibited CYP1A2 and CYP2D6 by 47% and 46%, respectively, and stimulated CYP3A4 by 56%.
    - Based on only modest inhibition of CYP1A and CYP2D6 at high concentrations, ARC1905 is not likely to cause drug-drug interactions by inhibiting CYP450 enzyme activity considering the low systemic exposure observed following IVT injection (mean C_{max} = 68.4 ng/mL) in the clinical trials.
- Weak binding of avacincaptad pegol to human serum albumin (HSA) and α1-acid glycoprotein (AGP) was observed at 15.6 µM (201 µg/mL). These results suggest that non-specific plasma protein binding of avacincaptad pegol is minimal.

5.2 Toxicokinetics

In the chronic repeat IVT dose toxicity studies in NZW rabbits and Beagle dogs with monthly dosing for 9 months (a total of 10 doses), mean plasma concentrations were ≤51.3 ng/mL in rabbits and ≤ 488.7 ng/mL in dogs. There was no accumulation with repeated dosing in rabbits. In dogs, plasma concentrations were considerably higher (~2-40x) on Day 253/255 (after 10 doses) compared to a single dose or 3 monthly doses at the mid and high dose. Co-administration of Lucentis® had no influence on ARC1905 plasma levels. See further details under Section 6.2 Repeat-Dose Toxicity of this review.

6 General Toxicology

6.1 Single-Dose Toxicity

Single-dose range finding studies by the IV route of administration were conducted in rats and monkeys. These studies were reviewed under the initial IND (Chen & Rivera, filed in DARRTS on 9-26-2008). Key findings, as noted in the IND nonclinical review, are listed below.

Single-Dose Range-Finding Study in Sprague-Dawley Rats (Study No. KSH00038)

Doses: 0 (saline control), 10, 26, 54, 100, 260, 540, and 800 mg/kg
Number/sex/group or timepoint (main study): 9/sex/group

- Mortality and decreased body weight were noted at 540 and 800 mg/kg.
- Clinical pathological changes were seen at ≥ 540 mg/kg including slight decreases of cholesterol, total protein and albumin levels, minimal decreases of

red blood cell parameters and platelet counts, and moderately higher total white blood cell counts.
- An increase in PT and APTT values were observed at ≥ 26 mg/kg.
- Histopathological examinations showed dose-dependent minimal to mild cytoplasmic vacuolation of resident and/or infiltrating mononuclear phagocytic cells in many tissues at ≥ 54 mg/kg and minimal bone marrow hypocellularity in females at 800 mg/kg.
- The dose of 26 mg/kg was selected as the NOAEL despite the increase in APTT.
- At the NOEL, the $AUC_{0\text{-last}}$ was 2658 or 1933 µg•hr/mL, and the C_{max} was 364 or 397 µg/mL in males or females, respectively.

Single-Dose Range-Finding Study in Cynomolgus Monkeys (Study No. KSH00033)
Doses: 0 (saline control), 2.9, 8.6, 28.7, 86.2, or 287 mg/kg
Number/sex/group or timepoint (main study): 1

- ARC1905 was associated with changes in several hematological parameters (decreased RBC, hematocrit, and hemoglobin, increased platelets) and clinical chemistry parameters (decreased cholesterol, albumin, globulin, and phosphorus) at ≥ 86.2 mg/kg or at 287 mg/kg.
- ARC1905 caused an increase in APTT values at ≥ 86.2 mg/kg.
- No drug induced activation of complement, as assessed by plasma C3a and Bb values, was noted. Some C3a values exceeded the normal range of ≤ 368 ng/mL, suggesting a possible activation of complement. However, there was not a clear dose- or time-dependent response, and therefore the increases may be unrelated to ARC1905.
- Dose-dependent minimal to moderate cytoplasmic vacuolization of resident and/or infiltrating mononuclear phagocytic cells was observed at ≥ 86.2 mg/kg in several tissues.
- The NOAEL was 28.7 mg/kg (C_{max} of 202-215 µg/mL; AUC of 3569-3869 µg•hr/mL).
- This dose was also identified as a pharmacologically active dose showing ≥ 99% inhibition of complement activity through 0.5 hour after the end of infusion.
- ARC1905 did not activate complement at the doses evaluated.

6.2 Repeat-Dose Toxicity

Repeat-dose ocular toxicity studies were conducted in New Zealand White rabbits and Beagle dogs. An interim report (with data up to week 13) was submitted under the initial IND. The final report for these studies was previously submitted to IND 77902 under SDN-16 and formally reviewed (Rivera, filed in DARRTS on 10-13-2015). The SDN-16 reviews are copied below with additional comments showed in italics.

Study title: A 1-Month (Single-Dose) and 9-Month (Ten-Dose) Toxicity Study of ARC1905 Given by Intravitreal Injections to Rabbits with and without Combination Treatment with Lucentis™

Study no.:	XGL00005
Study report location:	DocuBridge Module 4.2.3.2 \\CDSESUB1\EVSPROD\nda217225\0004\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\xgl00005\xgl00005.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Jan 4, 2008
GLP compliance:	Yes, with the following exceptions: • Electroretinography data were collected with an instrument that was not fully validated according to 21 CFR Part 11. • The testing for the generation of the Certificate of Analysis for the bulk test article was not performed under GLP or GMP.
QA statement:	Yes
Drug, lot #, and % purity:	ARC1905, lot # X01B07001N, 79.3% pure

Key Study Findings

- Minimal to moderate focal vacuolation was noted in the ganglion cell layer of the retina at the high dose (1.5 mg/eye ± 0.3 mg/eye Lucentis™) as early as the first termination timepoint (Day 4). *The vacuolation was not present in recovery necropsies.*
- Inflammation within the vitreous humor and, in some cases, panuveitis was noted with higher frequency in animals receiving the combination of 1.5 mg/eye ARC1905 + 0.3 mg/eye Lucentis™ starting at Week 5 (after the 2nd IVT dose) and increasing in severity with continued dosing. The inflammation was associated with alterations in ERG parameters and changes in IOP.
- Other findings observed in animals receiving 1.5 mg/eye ARC1905 + 0.3 mg/eye Lucentis™ included increased incidence of corneal opacities, vacuolar degeneration of the optic tract in the brain, marked diffuse retinal atrophy, fibrinous accumulation in the anterior and posterior chambers, cataract, chronic inflammation of the choroid, and marked posterior chamber abscess formation. *These findings were limited to the animals with severe inflammation and could be related to an immune reaction to Lucentis™. However, the lack of evaluation of a Lucentis™ alone group precludes a definitive assessment of a potential interaction between both molecules in the development of the inflammatory response.*
- ARC1905 was detected in the systemic circulation at low levels (≤ 54.7 ng/mL).
- There were no systemic toxicities.

- *Based on the finding of focal retinal vacuolation,* the NOEL for ocular toxicity was the mid dose, 0.5 mg/eye ARC1905.
- *The vacuolation was mostly of mild severity, reversible, and not associated with histopathological adverse changes (i.e., retinal degeneration, inflammation, necrosis) or noticeable effects on ERG measurements, therefore, it appears not to be adverse. As such, the NOAEL for ARC1905 monotherapy is the high dose, 1.5 mg/eye.*

Methods

Doses:	See Experimental Design table below.
Frequency of dosing:	Monthly on Days 1, 29, 57, 85, 113, 141, 169, 197, 225, and 253 (males and recovery animals) or 256 (females)
Route of administration:	IVT to both eyes
Dose volume:	50 µL/injection/eye
Formulation/Vehicle:	Sterile phosphate-buffered saline (PBS)
Species/Strain:	New Zealand White rabbits
Number/Sex/Group:	2-9 (see table below) Two rabbits/sex from Group 1 (control) and Group 5 (1.5 mg/eye ARC1905) were retained for a 4-week recovery period.
Age:	6 months old
Weight:	3.7-4.2 kg for males; 3.6-4.3 kg for females
Satellite groups:	Group 7 (see table below)
Unique study design:	A combination group with Lucentis™ (Group 6) was evaluated. Lucentis™ was administered by IVT injection at a volume of 30 µL/eye. The doses of ARC1905 and Lucentis™ were administered 1 hr ± 10 min apart. Control Group 1 received one IVT injection at each dosing day, whereas control Group 2 received 2 IVT injections in a manner analogous to Group 6. The study included 4 termination times: • Week 1 (3 days after the 1st dose) • Week 5 (recovery following the 1st dose) • Week 37 (3 days after the last dose) • Week 41 (recovery from last dose)
Deviation from study protocol:	None with an impact in the interpretation of the study

Study Design - 1-Month and 9-Month Ocular Toxicity Study in Rabbits

Group Number	Number/Sex/Group	Treatment	Dose Level (mg/eye)	Week of Necropsy (Number Euthanized/Sex/Group)			
				1[f]	5[g]	37[h]	41
1	9	Vehicle Control[a]	0	2	2	3	2
2	2	Vehicle Control[a]	0			2	
3	5	ARC1905[b]	0.15[d]	2		3	
4	5	ARC1905[b]	0.5[d]	2		3	
5	9	ARC1905[b]	1.5[d]	2	2	3	2
6	7	ARC1905 + Lucentis[c]	1.5 + 0.3[e]	2	2	3	
7[i]	3 males only	ARC1905 + Vehicle Control	1.5 + 0[j]				

[a] Doses of vehicle control were given at the same dosing volume and schedule as ARC1905. For Group 2, two doses of vehicle control article (PBS) were given on each dosing day in a manner analogous to Group 6, to control for the effects of two consecutive intravitreal injections on each dosing day.
[b] ARC1905 was administered every four weeks (i.e., Weeks 1, 5, 9, 13, 17, 21, 25, 29, 33, and 37).
[c] Lucentis™ was administered on the same days as ARC1905, one hour (± 10 minutes) after the injection of ARC1905.
[d] The ARC1905 doses shown are expressed in terms of the oligonucleotide content. However, the total weight of the test article was approximately 5.1 times that of the oligonucleotide component, and a correction factor of 5.32 was applied for this.
[e] ARC1905 and Lucentis™ doses, respectively.
[f] Animals terminated three days after the first dose.
[g] Animals terminated four weeks after the first dose (no second dose).
[h] Animals terminated three days after the last dose.
[i] These animals were used for a non-GLP assessment of the effect of the concurrent dosing (which was applied to Groups 2 and 6) on intraocular pressure, prior to commencement of the main part of the study. This assessment was limited to dosing and intraocular pressure (IOP) measurements and was documented in the study records. This investigation was completed prior to initiation of Groups 1 through 6, and the animals were removed from study without necropsy.
[j] The second injection for Group 7 (IOP test) was 30 µL of PBS.

Observations and Results

Mortality (Twice daily)

There were 3 deaths considered unrelated to treatment. One low dose male (0.15 mg/eye) and one mid-dose female (0.5 mg/eye) were found dead on Day 25 and 197, respectively. Both of these early deaths occurred on days in which the animals were anesthetized for study procedures, and the cause of death for both appeared to be anesthesia related. A Group 5 female was euthanized and discarded without further examination on Day 235 due to a dosing error.

Clinical Signs (Once daily)

The following clinical observations were seen across dose groups including controls: redness around the eye/eyelids, bloodshot eyes, red discoloration of the conjunctiva, protrusion of the nictitating membrane, pupil size dilated, pupillary reflex diminished, eye protruding, excessive lacrimation, material around eyes, and swelling around the eyes. The clinical signs were generally seen at the day of dosing and a few days postdose, except for dilated pupils and diminished pupillary reflex that persisted for a longer period.

As these findings were also observed in control groups, they were considered most likely related to the dosing procedure. However, discolored conjunctiva showed a higher incidence in Group 6 animals (1.5 mg/eye ARC1905 + 0.3 mg/eye Lucentis™) compared to both control groups. Discolored conjunctiva did not persist until the end of the dosing period (observed only until Day 170 in males and Day 229 in females). Dilated pupil size and diminished pupillary reflex showed increased incidence in all ARC1905-treated groups in males (not dose related) and in Group 6 females. These findings were not observed during recovery in Group 5 animals (only ARC1905-treated group evaluated).

Observations that were seen only in Group 6 included eccentric pupil (one male on Days 100-104), eye discolored (one male on Days 65-80), eye small (one male and on female from Days 230-256), and ocular discharge (one female from Days 202-211).

Corneal opacity was noted in both eyes of one Group 6 male (#4489) starting on Day 60, one Group 6 female (#4490) in the left eye starting on Day 226 and in both eyes starting on Day 250, one Group 6 female (#4492) in the left eye starting on Day 140 and on both eyes starting on Day 242, and one Group 6 female (#4494) in the right eye starting on Day 230. Corneal opacity was also noted in one Group 1 control female (# 4432; receiving a single IVT injection at each dosing day) from Days 58-212. However, the increased incidence in Group 6 and lack of a similar finding in control Group 2 (receiving 2 IVT injection at each dosing day), suggest that the finding may have a relationship to treatment.

The reversibility of corneal opacity was not assessed as Group 6 was not evaluated during recovery.

Body Weights (Day 1, every 2 weeks after Day 1, prior to fasting for those animals being submitted for necropsy, and prior to necropsy)

No test article-related effects

Feed Consumption (Qualitatively estimated daily)

No test article-related effects

Ocular Scoring (Pretest, Day 3, during Weeks 5, and 2 to 3 days after dosing on Weeks 13, 25, and 37, and during 40 [recovery])

Redness and chemosis of the conjunctiva were seen across groups and were considered most likely related to manipulations of the eyes as part of the dosing procedures. The severity was generally graded 1, with occasional occurrences of 2.

In Group 6 animals, corneal opacity was noted in the right eye (severity of 3) of one male (#4489) on Week 13 with progression to both eyes (severity of 4) by Week 37, in both eyes of one female (#4490) on Week 37 (severity of 3 and 4), and in the left eye (severity of 3) of one female (#4492) starting on Week 25 and in the right eye (severity of 3) on Week 37. One control female (Group 1; # 4432) also had corneal opacity of the left eye (severity of 2) starting on Week 13 with the same severity throughout the rest of the study.

Ophthalmoscopy (Predose, immediately postdose at each dose, during Week 4 [for animals submitted for necropsy at Week 5], and 2-3 days after dosing on Weeks 1, 4, 13, 25, and 37)

Inflammation within the vitreous humor and, in some cases, panuveitis were noted with higher frequency in animals receiving 1.5 mg/eye ARC1905 + 0.3 mg/eye Lucentis™ (Group 6), starting on Week 5 (after the 2nd dose) with higher severity as study progressed. Two out of 7 males (# 4489 and # 4493) and 3 out of 7 females (# 4490, # 4492, and # 4494) were affected.

The individual findings observed in Group 6 animals during Weeks 21-37 are shown below (copied from the Study Report):

Table 9: Individual Ophthalmic Examinations in Group 6 (1.5 mg/eye ARC1905 + 0.3 mg/eye Lucentis™) – **Weeks 21-37 – Ocular Toxicity Study in Rabbits**

Males:

Group/ Sex	Animal Number	Week 21 - Predose 1st Dose	Week 21 - Postdose 1st Dose	Week 21 - Predose 2nd Dose	Week 21 - Postdose 2nd Dose
6m	4481	.	.	.	.
	4483	.	.	.	.
	4485	.	.	.	.
	4487	.	.	.	.
	4489	No Pupillary Light Response, 360 Degree Corneal Vascularization, Complete Filling of Anterior Chamber with Fibrin and Hypopyon, No Dazzle, and Fundus Not Seen, Both Eyes	.	.	.
	4491	Normal	Normal	Normal	Normal
	4493	Multifocal White Pinpoint Anterior Vitreal Opacities, Both Eyes	Multifocal White Pinpoint Anterior Vitreal Opacities, Both Eyes	Multifocal White Pinpoint Anterior Vitreal Opacities, Both Eyes	Multifocal White Pinpoint Anterior Vitreal Opacities, Both Eyes

Group/ Sex	Animal Number	Week 25 - Predose	Week 25 - Postdose	Week 25 - Postdose 2nd Dose	Week 25
6m	4481	.	.	.	.
	4483	.	.	.	.
	4485	.	.	.	.
	4487	.	.	.	.
	4489	Mature Cataract and Posterior Synechia, Both Eyes	.	.	Mature Cataract and Posterior Synechia, Both Eyes; Anterior Lens Displacement, Right Eye
	4491	Normal	Normal	Normal	Normal
	4493	Diffuse Pinpoint Anterior Vitreal Opacities, Both Eyes	Diffuse Pinpoint Anterior Vitreal Opacities, Both Eyes	Diffuse Pinpoint Anterior Vitreal Opacities, Both Eyes	Hypopyon and Fibrin, Left Eye; Complete Anterior Vitreal Opacification, Both Eyes

Group/ Sex	Animal Number	Week 29 - Predose	Week 29 - Postdose	Week 29 - Predose 2nd Dose	Week 29 - Postdose 2nd Dose
6m	4481	.	.	.	.
	4483	.	.	.	.
	4485	.	.	.	.
	4487	.	.	.	.
	4489	No Pupillary Light Response, No Dazzle, Posterior Synechia, and Mature Cataract, Both Eyes; Fundus Not Observable	.	.	.
	4491	Normal	Normal	.	.
	4493	Multifocal to Diffuse Pinpoint and Larger White Anterior Vitreal Opacities, Both Eyes	Multifocal to Diffuse Pinpoint and Larger White Anterior Vitreal Opacities, Both Eyes	Multifocal to Diffuse Pinpoint and Larger White Anterior Vitreal Opacities, Both Eyes	Multifocal to Diffuse Pinpoint and Larger White Anterior Vitreal Opacities, Both Eyes

Group/ Sex	Animal Number	Week 37 - Postdose	Week 37 - Predose 2nd Dose	Week 37 - Postdose 2nd Dose	Week 37
6m	4481	.	.	.	.
	4483	.	.	.	.
	4485	.	.	.	.
	4487	.	.	.	.
	4489	.	.	.	Posterior Synechia, Cataract, Both Eyes
	4491	Normal	Normal	Normal	Normal
	4493	.	.	.	Complete Retinal Detachment, Both Eyes

Dose Level: Group 1 - 0 (Vehicle Control) mg/eye Group 2 - 0 (Vehicle Control) mg/eye
Group 3 - 0.15 (ARC1905) mg/eye Group 4 - 0.5 (ARC1905) mg/eye
Group 5 - 1.5 (ARC1905) mg/eye Group 6 - 1.5 + 0.3 (ARC1905 + Lucentis™) mg/eye

Females:

Group/ Sex	Animal Number	Week 21 - Predose 1st Dose	Week 21 - Postdose 1st Dose	Week 21 - Predose 2nd Dose	Week 21 - Postdose 2nd Dose
6f	4482	.		.	.
	4484	.		.	.
	4486	.		.	.
	4488	.		.	.
	4490	Syneresis, White Linear and Pinpoint White Opacities in Anterior Vitreous and Focal Accumulation of Debris in Central Anterior Vitreous, Both Eyes	Syneresis, White Linear and Pinpoint White Opacities in Anterior Vitreous, and Focal Accumulation of Debris in Central Anterior Vitreous, Both Eyes	Syneresis, White Linear and Pinpoint White Opacities in Anterior Vitreous, and Focal Accumulation of Debris in Central Anterior Vitreous, Both Eyes	Syneresis, White Linear and Pinpoint White Opacities in Anterior Vitreous, and Focal Accumulation of Debris in Central Anterior Vitreous, Both Eyes
	4492	No Dazzle, Mature Cataract, and Posterior Synechia, Left Eye; Multifocal White Pinpoint Anterior Vitreal Opacities, Right Eye	No Dazzle, Mature Cataract, and Posterior Synechia , Left Eye; Multifocal White Pinpoint Anterior Vitreal Opacities, Right Eye	No Dazzle, Mature Cataract, and Posterior Synechia , Left Eye; Multifocal White Pinpoint Anterior Vitreal Opacities, Right Eye	No Dazzle, Mature Cataract, and Posterior Synechia , Left Eye; Multifocal White Pinpoint Anterior Vitreal Opacities, Right Eye
	4494	Multifocal White Pinpoint Anterior Vitreal Opacities, Both Eyes	Multifocal White Pinpoint Anterior Vitreal Opacities, Both Eyes	Multifocal White Pinpoint Anterior Vitreal Opacities, Both Eyes	Multifocal White Pinpoint Anterior Vitreal Opacities, Both Eyes

Group/ Sex	Animal Number	Week 25 - Predose	Week 25 - Postdose	Week 25 - Postdose 2nd Dose	Week 25
6f	4482	.	.	.	.
	4484	.	.	.	.
	4486	.	.	.	.
	4488	.	.	.	.
	4490	Complete Anterior Vitreal Opacification, Both Eyes	.	.	Complete Anterior Vitreal Opacification, Both Eyes
	4492	Mature Cataract and Posterior Synechia, Left Eye; Complete Anterior Vitreal Opacification, Right Eye	.	.	Hypopyon, Fibrin, Posterior Synechia, and Complete Anterior Vitreal Opacification, Right Eye; Mature Cataract, Left Eye
	4494	Multifocal Light Pinpoint Anterior Vitreal Opacity, Both Eyes	Multifocal Light Pinpoint Anterior Vitreal Opacity, Both Eyes	Multifocal Light Pinpoint Anterior Vitreal Opacity, Both Eyes	Diffuse White Anterior Pinpoint Opacities, Both Eyes

Group/ Sex	Animal Number	Week 29 - Predose	Week 29 - Postdose	Week 29 - Predose 2nd Dose	Week 29 - Postdose 2nd Dose
6f	4482	.	.	.	.
	4484	.	.	.	.
	4486	.	.	.	.
	4488	.	.	.	.
	4490	Linear White Trans Vitreal Opacities and Complete Retinal Detachment, Both Eyes	.	.	.
	4492	Posterior Synechia, Mature Cataract and Left Eye; Diffuse Vitreal Opacification with White Linear Opacities and Retinal Detachment, Right Eye	.	.	.
	4494	Multifocal Pinpoint Anterior Vitreal Opacities, Both Eyes	Multifocal Pinpoint Anterior Vitreal Opacities, Both Eyes	Multifocal Pinpoint Anterior Vitreal Opacities, Both Eyes	Multifocal Pinpoint Anterior Vitreal Opacities, Both Eyes

Group/ Sex	Animal Number	Week 33 - Predose	Week 33 - Postdose	Week 33 - Postdose 2nd Dose	Week 37 - Predose
6f	4482	.	.	.	.
	4484	.	.	.	.
	4486	.	.	.	.
	4488	.	.	.	.
	4490	Mature Cataract and Posterior Synechia, Left Eye; Anterior Vitreal Opacification and Complete Retinal Detachment, Right Eye	.	.	Mature Cataract, Both Eyes
	4492	Mature Cataract and Posterior Synechia, Left Eye; Anterior Vitreal Opacification and Complete Retinal Detachment, Right Eye	.	.	Mature Cataract, Both Eyes
	4494	Posterior Synechia and Hyper Mature Cataract, Right Eye; Diffuse White Pinpoint Vitreal Opacities, Left Eye	Posterior Synechia and Hyper Mature Cataract, Right Eye; Diffuse White Pinpoint Vitreal Opacities, Left Eye	Posterior Synechia and Hyper Mature Cataract, Right Eye; Diffuse White Pinpoint Vitreal Opacities, Left Eye	Complete Retinal Detachment, Left Eye; Mature Cataract, Right Eye

Group/ Sex	Animal Number	Week 37 - Postdose	Week 37 - Predose 2nd Dose	Week 37 - Postdose 2nd Dose	Week 37
6f	4482	.	.	.	.
	4484	.	.	.	.
	4486	.	.	.	.
	4488	.	.	.	.
	4490	.	.	.	Mature Cataract, Both Eyes
	4492	.	.	.	Mature Cataract, Both Eyes
	4494	.	.	.	Posterior Synechia, Diffuse White Pinpoint Vitreal Opacities, Left Eye; Cataract, Right Eye Eye; Posterior Synechia, Right Eye; Retinal Detachment, Left Eye

Dose Level: Group 1 - 0 (Vehicle Control) mg/eye
Group 2 - 0 (Vehicle Control) mg/eye
Group 3 - 0.15 (ARC1905) mg/eye
Group 4 - 0.5 (ARC1905) mg/eye
Group 5 - 1.5 (ARC1905) mg/eye
Group 6 - 1.5 + 0.3 (ARC1905 + Lucentis™) mg/eye

Reversibility was not assessed in the combination group. The Applicant stated this trend was suggestive of the development of an immune response to Lucentis™ (a human protein, which is likely to be immunogenic in rabbits). However, the lack of evaluation of a Lucentis™ alone group precludes a definitive assessment of a potential interaction between both molecules in the development of the inflammatory response.

Some sporadic signs of inflammation were seen in individual animals of Groups 1-5. As noted by the Applicant, these changes were likely associated with multiple IVT injections.

IOP (Pretest and within 2 to 3 days after dosing on Weeks 1, 4 [prior to Dose 2 and Week 5 euthanasia], 13, 25, and 37, and during Week 40 [recovery])

Changes in IOP were observed in Group 6 animals (1.5 mg/eye ARC1905 + 0.3 mg/eye Lucentis™) that showed ocular inflammation. The changes are likely secondary to the inflammation observed in these animals.

- Male # 4493 had lower IOP in the right eye compared to the range observed in controls (6.0-7.0 mmHg *vs.* a lowest of 7.5 mmHg in concurrent controls) on Week 25. On Week 37, this animal showed increased IOP in both eyes (35-42 mmHg *vs.* a highest of 25.5 mmHg in concurrent controls).

- Female # 4490 showed decreased IOP in both eyes on Week 13 (5.5-7.5 mmHg *vs*. a lowest value of 9.5 mmHg in concurrent controls). Values within normal range were observed afterwards.

- Female # 4492 showed decreased IOP in the right eye on Week 13 (6.5-7.0 mmHg *vs.* a lowest value of 9.5 mmHg in concurrent controls). Values within normal range were observed afterwards.

- Female # 4494 showed decreased IOP in the right eye on Week 37 (5.0-5.5 mmHg *vs.* a lowest value of 11.5 mmHg in concurrent controls).

Electroretinography (ERG) (Prestudy and within 2 to 3 days after dosing on Weeks 1, 4 [prior to Dose 2 and Week 5 euthanasia], 13, 25, and 37, and during Week 40 [recovery])

The data showed high within-group variability for several parameters, making it difficult to determine a test article-related effect. There was a decrease in mean a-wave and b-wave amplitude and/or longer implicit times particularly in Group 6 females (ARC1906 + Lucentis^{TM}) at Weeks 25-37 under scotopic and/or photopic conditions (the Applicant considered the effects were mainly noted under scotopic conditions for Group 6 animals on Week 37). Some values were statistically significantly different from controls ($p \leq 0.05$). As noted by the Applicant, the ERG changes may be related to the inflammation observed in these animals.

The Applicant indicated the ERG data showed no differences between groups up to Week 13 except for Group 6 animal #4489, which showed a reduction in a- and b-wave amplitude in both eyes during Week 13. This reviewer could not definitively determine a treatment related effect in this animal given the high within-group variability.

Hematology and Coagulation (Pretest, Week 1 [prior to necropsy], Week 5 [prior to the 2nd dose and the recovery sacrifice], Week 13 [within two days after the 4th dose], Week 25 [within 2 days after the 7th dose], Week 37 [within 2 days after the 10th dose], and Week 41 [recovery animals])

No test article-related effects

Clinical Chemistry (Same as Hematology)

No test article-related effects

Gross Pathology (Weeks 1 [3 days after the 1st dose], Week 5 [recovery after the 1st dose], 37 [3 days after the last dose], and 41 [recovery])

No test article-related effects

Organ Weights (Adrenal glands, brain, heart, kidney, liver, lung, ovary, spleen, testis, and thymus)

No test article-related effects

Histopathology (Performed on the eyes from all animals in all groups at all sacrificed timepoints. The standard battery of systemic tissues was processed and examined for all animals in Groups 1, 5, and 6 euthanized at Week 1 and for remaining animals in Groups 1, 2, 5, and 6 euthanized at Week 37. For the animals found dead, histopathology was performed only on the eyes.)

Adequate Battery - Yes

Peer Review - No

Histological Findings - Minimal to moderate vacuolation (focal) in the ganglion cell layer of the retina (without notable thickening of the retina) was observed in one or both eyes of one Group 5 male, one Group 6 male, both Group 5 females (1.5 mg/eye ARC1905), and one Group 6 female (1.5 mg/eye + Lucentis™) on Day 4 termination (3 days after the 1st dose). The finding was not present on Day 29 (recovery period of 4 weeks after the 1st dose). On Week 37, mild retinal vacuolation was observed in 5 of 6 eyes in Group 5 females. The finding was again reversible following a 4-week recovery period (Day 281). It was stated in the study report that the finding was not observed in Group 6 animals on Week 37 due to diffuse retinal atrophy *precluding detection of other changes* (see below).

Focal retinal vacuolation was characterized by the presence of discrete round empty spaces between fibers and cells in the ganglion cell layer without notable thickening of the affected retina. As stated in the Study Report, vacuolation of this nature has been observed in various tissues with other large molecular weight PEGylated products, including PEGylated aptamers, and when observed, has not been associated with adverse morphological or functional changes.

The incidence of retinal vacuolation at Day 4 and Week 37 are presented in Table 9 below (excerpts of Table 2.6.7.7-1, Module 2.6.7 Toxicology Tabulated Summary, with a correction by this reviewer)

Focal retinal atrophy (mild to moderate), characterized by loss of cells from the inner nuclear layer and outer nuclear layer, was observed in both eyes of 1 of 2 Group 6 males at Day 4 termination. Focal retinal atrophy (minimal to marked) was also observed in controls and in ARC1905-treated groups without a dose-relationship during Week 37. The finding was present in controls (2 of 4 eyes in males and in 1 of 4 eyes in females) during the recovery period; no Group 5 (1.5 mg/eye ARC1905) eyes showed

the finding. As noted by the Applicant, the finding may be incidental or may have been caused by mechanical damage by the injection procedure. *The focal retinal atrophy was not observed in animals with retinal vacuolation.*

The following findings were observed in Group 6 animals (1.5 mg/eye ARC1905 + 0.3 mg/eye Lucentis™) during Week 37: vacuolar degeneration of the optic tract in the brain in 2 of 3 males, and in 3 of 3 females; marked diffuse retinal atrophy in both eyes, characterized by essentially total absence of retinal cell layers in one male and in all females; fibrinous accumulation in the anterior chamber (minimal to moderate) and posterior chamber (moderate to marked) in one eye of one male and all females (5 of 6 eyes); cataract (minimal to moderate) in both eyes of one male and all females (5 of 6 eyes); marked chronic inflammation of the choroid in one eye of one male; and marked posterior chamber abscess formation in one eye of one female. These findings were present in the same animals with severe ocular inflammation observed by ophthalmoscopy.

Table 10: Incidence of Microscopic Findings of Retinal and Optic Nerve Vacuolation -1-Month and 9-Month Ocular Toxicity Study in Rabbits

Day 4

Noteworthy Findings												
Group:	**1**		**2**		**3**		**4**		**5**		**6**	
Monthly Dose (mg/eye):	**0 (Control)[b]**		**0 (Control)[b]**		**0.15**		**0.5**		**1.5**		**1.5+0.3[c]**	
Number of Animals:	**M: 9**	**F: 9**	**M: 2**	**F: 2**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 9**	**F: 9**	**M: 7**	**F: 7**
Histopathology:												
Week 1 Euthanasia												
Eye (Left; No. examined)	2	2	-	-	2	2	2	2	2	2	2	2
Focal retinal vacuolation	-	-	-	-	-	-	-	-	1	2	1	1
Eye (Right; No. examined)	2	2	-	-	2	2	2	2	2	2	2	2
~~Week 37~~ Euthanasia												
Focal retinal vacuolation	-	-	-	-	-	-	-	-	1	2	1	-
Minimal	-	-	-	-	-	-	-	-	0	0	1	-
Mild	-	-	-	-	-	-	-	-	1	1	0	-
Moderate	-	-	-	-	-	-	-	-	0	1	0	-

Note: Week 37 was crossed out because data belongs to Day 4 histopathology evaluation.

Day 37

Group:	1		2		3		4		5		6	
Monthly Dose (mg/eye):	0 (Control)[b]		0 (Control)[b]		0.15		0.5		1.5		1.5+0.3[c]	
Number of Animals:	M: 9	F: 9	M: 2	F: 2	M: 5	F: 5	M: 5	F: 5	M: 9	F: 9	M: 7	F: 7
Brain (No. examined)	3	3	2	2	0	0	0	0	3	3	3	3
Bilateral vacuolar degeneration of the optic tract	-	-	-	-	-	-	-	-	-	-	1	3
Mild	-	-	-	-	-	-	-	-	-	-	1	1
Moderate	-	-	-	-	-	-	-	-	-	-	0	2
Unilateral vacuolar degeneration of the optic tract	-	-	-	-	-	-	-	-	-	-	1	0
Mild	-	-	-	-	-	-	-	-	-	-	1	0
Eye (Left; No. examined)	3	3	2	2	2	3	3	2	3	3	3	3
Focal retinal vacuolation	-	-	-	-	-	-	-	-	-	2	-	-
Mild	-	-	-	-	-	-	-	-	-	2	-	-
Eye (Right; No. examined)	3	3	2	2	2	3	3	2	3	3	3	3
Focal retinal vacuolation	-	-	-	-	-	-	-	-	-	3	-	-
Mild	-	-	-	-	-	-	-	-	-	3	-	-

Note: *Table not included in initial nonclinical review filed for SDN-16.*

Following a one-month recovery period (Day 41 sacrifice), there were no test article-related ocular findings *at ARC1905 high dose (only group evaluated)*.

On Week 37 microscopic observations, two females each in Group 5 (1.5 mg/eye ARC1905) and Group 6 (1.5 mg/eye ARC1905 + 0.3 mg/eye Lucentis™) had mild or moderate follicular hemorrhage in the ovaries. The lack of a similar finding in control and lower dose groups suggests the finding may be ARC1905 related. However, a similar finding was not observed in the embryofetal developmental toxicity studies in rabbits or in the dog 9-month repeated-dose IVT toxicity at higher systemic exposures. In addition, products with a similar pharmacology (inhibition of C5 function), did not show effects in mating or fertility (see labels for Soliris® (eculizumab], Tavneos® [avacopan], Ultomiris® [ravulizumab]). It appears that the finding is of no clinical relevance.

Toxicokinetics (Following doses 1, 3, and 10 [Days 1, 57, and 253/256, respectively] at 0.5, 3, 8, 24, 72, and 144 hours postdose)

ARC1905 was detected in the systemic circulation. Occasional samples from Group 3 animals (0.15 mg/eye) had quantifiable levels of ARC1905 marginally above the lower limit of quantification (LLOQ: 1.7 ng/mL). Most of the samples from Group 4 animals (0.5 mg/eye) and all samples from the higher dose groups had quantifiable levels of ARC1905 (≤54.7 ng/mL). The levels were sustained through 144 hours (7 days) after IVT injection, suggesting slow release from the eye. No consistent differences were observed between Groups 5 and 6 (i.e., with and without co-administration of Lucentis™), indicating that Lucentis™ had no influence on the uptake

of ARC1905 into plasma. There was no accumulation with repeated dosing. The mean plasma concentrations are shown in the following table.

Table 11: Mean ARC1905 Concentration in Plasma of Rabbits (ng/mL) – Chronic Ocular Toxicity Study (ng/mL)

Group No.	Treatment	Time Post-Injection (hours)					
		0.5	3	8	24	72	144
Study Day 1 (Dose 1)							
1	Control	ND	BLQ	ND	ND	ND	ND
2	Control*	ND	BLQ	ND	ND	ND	ND
3	ARC1905, 0.15 mg/eye	BLQ**	BLQ	BLQ	BLQ	BLQ	ND
4	ARC1905, 0.5 mg/eye	BLQ	BLQ	8.2	6.8	7.2	5.4
5	ARC1905, 1.5 mg/eye	BLQ	6.5	26.8	33.2	19.4	12.3
6	ARC1905, 1.5 mg/eye + Lucentis™	BLQ	9.9	26.2	36.8	22.4	14.5
Study Day 57 (Dose 3)							
1	Control	ND	BLQ	ND	ND	ND	ND
2	Control*	ND	BLQ	ND	ND	ND	ND
3	ARC1905, 0.15 mg/eye	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
4	ARC1905, 0.5 mg/eye	BLQ	BLQ	7.5	12.0	13.5	9.5
5	ARC1905, 1.5 mg/eye	3.5	13.8	32.3	51.3	31.7	22.8
6	ARC1905, 1.5 mg/eye + Lucentis™	6.3	23.6	38.6	54.7	51.4	14.5
Study Day 253 or 256 (Dose 10)							
1	Control	ND	BLQ	ND	ND	ND	ND
2	Control*	ND	BLQ	ND	ND	ND	ND
3	ARC1905, 0.15 mg/eye	BLQ	BLQ	BLQ	BLQ	BLQ	ND
4	ARC1905, 0.5 mg/eye	BLQ	BLQ	BLQ	5.9	12.0	ND
5	ARC1905, 1.5 mg/eye	BLQ	20.7	35.3	43.3	27.9	17.3
6***	ARC1905, 1.5 mg/eye + Lucentis™	BLQ	25.1	18.7	32.7	24.7	ND

ND - Not determined BLQ – Below the lower limit of quantification (3.4 ng/mL)

* Two injections (control for Group 6)

** For groups and time points where some animals had measurable values and some were BLQ, the group mean was determined as follows: If 50% or more of the animals in the group had values above the LLOQ, a value of ½ of the LLOQ (1.7 ng/mL) was assigned to all BLQ samples, and the group mean was calculated; however, if over half of the values were BLQ, then the group central tendency was represented as BLQ.

***N = 1

Dosing Solution Analysis

Samples from Doses 1, 5, and 10 were analyzed. The formulations were 90.5% to 110% of nominal.

Study title: A 1-Month (Single-Dose) and 9-Month (Ten Dose) Toxicity Study of ARC1905 Given by Intravitreal Injections to Beagle Dogs with and without Combination Treatment with Lucentis™

Study no.:	XGL0006
Study report location:	DocuBridge Module 4.2.3.2 \\CDSESUB1\EVSPROD\nda217225\0004\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\xgl00006\xgl00006.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Jan 4, 2008
GLP compliance:	Yes, with the following exceptions: • Electroretinography data were collected with an instrument that was not fully validated according to 21 CFR Part 11. • The testing for the generation of the Certificate of Analysis for the bulk test article was not performed under GLP or GMP.
QA statement:	Yes
Drug, lot #, and % purity:	ARC1905, lot # X01B07001N, 79.3% pure

Key Study Findings

- Minimal to moderate focal vacuolation was noted in the ganglion cell layer of the retina at the first termination time point (Day 4) at the mid dose (1.0 mg/eye) and high dose (3.0 mg/eye ARC1905 ± 0.5 mg/eye Lucentis™).
- With further dosing (Week 37), minimal to moderate focal retinal vacuolation was observed at all test article doses (± Lucentis™). Mild to diffuse retinal vacuolation was observed at the high dose (3.0 mg/eye ARC1905 ± 0.5 mg/eye Lucentis™).
- At Week 41, following a 4-week recovery period, focal retinal vacuolation persisted at the high-dose (3.0 mg/eye ARC1905 ± 0.5 mg/eye Lucentis™) but the severity had decreased, indicating partial reversibility.
- At Week 37, vacuolation (mild) of the optic tract in the brain was observed at 3.0 mg/eye ARC1905. This finding was reversible.
- *Based on the retinal vacuolation, there was no NOEL following a single or repeated IVT injections. Given the more diffuse retinal vacuolation observed at 3.0 mg and extension of the finding to the optic tract, a conservative approach was used to select the NOAEL. The NOAEL is considered to be 1.0 mg/eye even*

though optic tract vacuolation at 3.0 mg/eye was not associated with adverse histopathology or noticeable ERG findings.

- ARC1905 was detected in the systemic circulation (≤488.7 ng/mL) with plasma concentrations considerably higher (~2-40x) after 10 doses compared to a single or 3 monthly doses at the mid and high dose.
- There were no systemic findings except for a marginal increase in mean activated partial thromboplastin time (APTT) in both males and females receiving 3.0 mg/eye ARC1905 ± 0.5 mg/eye Lucentis™. The finding was not observed during recovery.

Methods

Doses:	See table below.
Frequency of dosing:	Monthly on Days 1, 29, 57, 83, 113, 141, 169, 197, 225, and 253 (males and recovery animals) or 255 (females)
Route of administration:	IVT to both eyes
Dose volume:	100 µL/injection/eye
Formulation/Vehicle:	Sterile phosphate-buffered saline (PBS)
Species/Strain:	Beagle dogs
Number/Sex/Group:	2-9 (see table below) Two dogs/sex from Group 1 (control) and Group 5 (1.5 mg/eye ARC1905) were retained for a 4-week recovery period.
Age:	5-6 months old
Weight:	6.3-8.6 kg for males; 6.3-9.3 kg for females
Satellite groups:	Group 7 (see table below)
Unique study design:	A combination group with Lucentis™ (Group 6) was evaluated. Lucentis™ was administered by IVT injection at a volume of 50 µL/eye. The doses of ARC1905 and Lucentis™ were administered 1-1.5 hours ± 15 min apart for the 1st dose and 25 ± 5 minutes apart for all other doses. Control Group 1 received one IVT injection at each dosing day, whereas control Group 2 received 2 IVT injections in a manner analogous to Group 6. The study included 4 termination times: • Week 1 (3 days after the 1st dose) • Week 5 (recovery following Dose 1) • Week 37 (3 or 4 days after the last dose) • Week 40 (recovery from last dose)
Deviation from study protocol:	None with an impact in the interpretation of the study

Study Design - 1-Month and 9-Month Ocular Toxicity Study in Dogs

Group Number	Number/Sex/Group	Treatment	Dose Level (mg/eye)	Week of Necropsy (Number Euthanized/Sex/Group)			
				1[f]	5[g]	37[h]	41
1	9	Vehicle Control[a]	0	2	2	3	2
2	2	Vehicle Control[a]	0			2	
3	5	ARC1905[b]	0.3[d]	2		3	
4	5	ARC1905[b]	1.0[d]	2		3	
5	9	ARC1905[b]	3.0[d]	2	2	3	2
6	7	ARC1905 + Lucentis™[c]	3.0[d] + 0.5[e]	2	2	3	
7[i]	1 male 1 female	ARC1905 + Vehicle Control	3.0[d] + 0[j]				

[a] Doses of vehicle control article were given at the same dosing volume and schedule as ARC1905. For Group 2, two doses of vehicle control article (PBS) were given on each dosing day in a manner analogous to Group 6, to Control for the effects of two consecutive intravitreal injections on each dosing day.
[b] ARC1905 was given in Weeks 1, 5, 9, 13, 17, 21, 25, 29, 33, and 37.
[c] Lucentis™ was administered on the same days as ARC1905, 60-90 minutes after the injection of ARC1905.
[d] The ARC1905 doses shown were expressed in terms of the oligonucleotide content. However, the total weight of the test article was approximately five times that of the oligonucleotide component, and a correction factor of 5.32 was used for weighing and dispensing the test material.
[e] ARC1905 and Lucentis™ doses, respectively.
[f] Animals were terminated 3 days after the first dose.
[g] Animals were terminated 4 weeks after the first dose (no second dose).
[h] Animals were terminated 3 or 4 days after the last dose.
[i] These animals were used for a non-GLP assessment of the effect of concurrent dosing (which was applied to Groups 2 and 6) on intraocular pressure, prior to commencement of the main part of the study. This assessment was limited to dosing and IOP measurements and was documented in the form of a dosing and IOP procedure memo. This investigation was completed prior to initiation of Groups 1-6, and the animals were removed from study without necropsy.
[j] The second injection for Group 7 (IOP test) was 50 µL of PBS.

Observations and Results

Mortality (Twice daily)

There were no mortalities considered test article related.

One Group 4 male (#4537) was found dead on Day 87. This animal had no remarkable clinical observations. Gross necropsy revealed a dark discoloration of the gall bladder. The apparent cause of death was believed to be an overdose of anesthesia.

One Group 1 female (#4510) and one Group 4 female (#4542) were euthanized on Day 146 because of an infection in one eye considered related to the injection procedures.

Clinical Signs (Once daily)

Test-article related signs were not apparent. Clinical signs seen across dose groups including controls, and most likely related to the dosing procedure, included bloodshot eyes, discoloration of the conjunctiva, conjunctivitis, corneal opacity, excessive lacrimation, eye discoloration, eye enlargement, material around the eye, and swelling around the eye.

Findings only observed in Group 6 males (3.0 mg/eye ARC1905 + 0.5 mg/eye Lucentis™) included redness around the eye/eyelids (within Days 79 to 141) and protrusion of the nictitating membrane (Days 3 to 4 only).

Body Weights (Pretest, Study Day 1, every two weeks after Study Day 1, prior to fasting for those animals being submitted for necropsy, and prior to necropsy)

No test article-related effects

Feed Consumption (Qualitatively estimated daily)

No test article-related effects

Ocular Scoring (Pretest, Day 3, during Week 5 prior to the second dose and termination, and 2 to 3 days after dosing on Weeks 13, 25, and 37, and during Week 40 [recovery])

Conjunctival redness was noted in controls and all ARC190-treated dogs and therefore, these findings appeared related to the dosing procedure.

Corneal opacity was observed in one male (# 4511) from control group (Group 1) from Day 172 onward, one female (# 4528) at 0.3 mg/eye (Group 3) from Day 88 onward, one male (# 4533) at 1.0 mg/eye (Group 4) on Day 3, and one male (#4561) at 3.0 mg/eye + 0.5 mg/eye Lucentis™ (Group 6) on Day 3. Except for Group 6 male # 4561, the finding was observed in one eye in all animals. The animals with corneal opacity on Day 3 were terminated on Week 1 scheduled euthanasia. Based on the incidence and presence in controls, the finding appeared associated with the injection procedure.

Ophthalmoscopy (Predose, immediately postdose for each injection, during Week 4 [for animals submitted for necropsy at Week 5], and 2-3 days after dosing on Weeks 1, 13, and 25, 1 day [females] and 2 days after dosing [males] on Week 37, and on Week 40 [recovery])

There were no test article-related findings. Findings attributed to the injection procedure included subconjunctival hemorrhage and edema, retinal detachment, anterior uveitis, panuveitis, pinpoint white vitreal opacities, and vitreal liquefaction (syneresis) observed in one or both eyes in all groups including controls.

The Applicant provided the following rationale for the findings of syneresis and pinpoint white vitreal opacities:

"As the study progressed, there was a trend towards syneresis (vitreal liquefaction) in all animals, regardless of group. Multiple IVT injections would be expected to elicit inflammation, and the resulting inflammation can cause liquefaction of the vitreous. Since almost all animals regardless of group demonstrated syneresis, this change is associated with the IVT injection procedure and not the test articles. Similarly, many animals, regardless of group, demonstrated white pinpoint IVT opacities. The density of IVT opacities varied between animals within a group, but there was no tendency towards an increase in IVT opacities associated with increasing doses of ARC1905. The IVT opacities observed most likely consisted of inflammatory cells and were associated with inflammation resulting from IVT injection."

Corneal dystrophy was observed in the left eye of control male # 4511 from Day 169 onward (right eye affected at later timepoints) and cataract was observed in the left eye of Group 3 female #4528 (with corneal opacities) from Day 225 onward.

IOP (**Pretest and within 3 days after dosing on Weeks 1, 4 [prior to Dose 2 and Week 5 euthanasia], 13, 25, and 37, and during Week 40 [recovery])**

No treatment related effects were noted. The decreased IOP (6.5-12.5 mmHg *vs.* concurrent control values of 12-25 mmHg) observed in the right eye in three Group 4 (1 mg/eye) males (#4533, #4537 and # 4539) at Week 1 and in the right eye of one Group 3 (0.3 mg/eye) male (#4531) and left eye of one Group 3 female (# 4528) at Week 13 was not observed with further dosing.

One Group 6 female (# 4572) had decreased IOP in both eyes on Week 25 (8.5-11 mmHg *vs*. 14.5-22 mmHg in concurrent controls). On Week 37, the values were on the low end of the concurrent control range, indicating recovery.

One Group 6 male (# 4571) had decreased IOP in both eyes on Week 37 (9.0-11.5 mmHg *vs*. 12.0-20 mmHg in concurrent controls).

Given the lack of an effect with continued dosing, the decrease in IOP appears unrelated to ARC1905 treatment.

ERG (Pretest and within 2 to 3 days postdose on Weeks 1, 4 [prior to Dose 2 and Week 5 euthanasia], 13, 25, and 37, and during Week 41 [recovery])

An increase in mean a-wave and b-wave implicit time was observed in both eyes in Group 5 females (3.0 mg/eye ARC1905) during recovery. Based on the lack of a similar effect during treatment, the finding appears unrelated to the test article. There was no distinct trend that would suggest any effect of the treatments on retinal conductivity. However, it must be kept in mind that the data are limited by the high within-group variability, making it difficult to determine a test article-related effect.

Electrocardiograms (ECG) (Pretest and Weeks 1, 37, and 40)

No test article-related effects

Hematology and Coagulation (Week 1 [prior to necropsy], Week 5 [prior to the 2nd dose and the recovery sacrifice], Week 13 [within two days after the 4th dose], Week 25 (within 2 days after the 7th dose), Week 37 (within 2 days after the 10th dose), and Week 41 (recovery animals)

At Week 13, 25, and 37, the mean APTT in both males and females receiving 3.0 mg/eye ARC1905 (Group 5) or 3.0 mg/eye ARC1905 + 0.5 mg/eye Lucentis™ (Group 6) was slightly higher compared to controls (mean of 20.8-25.0 sec *vs.* mean of 18.4-20.2 sec in controls). The mean APTT values were only marginally above the testing facility historical control range (15.4-23.1 sec). The finding was not observed during recovery.

Clinical Chemistry (Evaluated at the same timepoints as hematology)

A slightly but statistically significant increase in mean sodium and mean chloride levels was noted in all ARC1905-treated groups (i.e., Groups 3-6) during Week 13 (sodium: 150.0-152.8 mmol/L *vs.* 146-148 mmol/L in controls; chloride: 113.7-117.7 mmol/L *vs.* 112.4-113.0 mmol/L in controls). The mean values were only marginally above the laboratory historical control ranges (143-150 mmol/L for sodium and 108-114 mmol/L for chloride) with no additional pathological effects. As similar increases were not observed with further dosing, these changes were not considered toxicologically relevant.

Gross Pathology (Weeks 1 [3 days after the 1st dose], Week 5 [recovery after the 1st dose], Week 37 [3 or 4 days after the last dose], and Week 41 [recovery])

Red conjunctival discoloration (unilateral or bilateral) was observed in 1, 2, 2, 2, and 2 out of 4 animals/group in control (Group 1), 0.3 mg/eye (Group 3), 1 mg/eye (Group 4), 3 mg/eye (Group 5) and 3 mg/eye + 0.5 mg/eye Lucentis™ (Group 6), respectively, on Day 4. The finding was not present in the Day 29 necropsy (before the 2nd dose was given), indicating it was reversible. The finding was noted at Week 37 in 1 control male receiving 2 IVT doses of vehicle (Group 2), 1 Group 6 male, and in 1 Group 6 female. A microscopic correlate for this finding was not found, but the incidence suggests that it was unrelated to the test article and most likely related to the injection procedure.

Opaque corneal discoloration (unilateral) was observed in one Group 6 male (3 mg/eye ARC1905 + Lucentis™) and one Group 4 male (1.0 mg/eye) on Week 1 which correlated microscopically with the finding of mild acute inflammation in the anterior chamber. The finding was possibly related to the injection procedure as it was not noted with further dosing.

Organ Weights (Adrenal glands, brain, heart, kidney, liver, lung, ovary, spleen, testis, and thymus)

No test article-related effects

Histopathology (Performed on the eyes from all animals in all groups at all sacrificed time-points. The standard battery of systemic tissues was processed and examined for all animals in Groups 1, 5, and 6 euthanized at Week 1 and for remaining animals in Groups 1, 2, 5, and 6 euthanized at Week 37. For the unscheduled deaths, histopathology was performed on the eyes, with full battery for the control female.)

Adequate Battery - Yes

Peer Review – No

Histological Findings - Similar to findings in rabbits, minimal to moderate focal vacuolation in the ganglion cells layer of the retina was noted on Day 4 in one or both eyes of all high-dose animals (3.0 mg/eye ± 0.5 mg/eye Lucentis™) (Table 11). Mild focal retinal vacuolation was also noted in one mid-dose female (1.0 mg/eye). The vacuolation was characterized by the presence of discrete empty spaces between fibers and cells in the ganglion cell layer without notable thickening of the retina. The finding was not present on Day 29 (4-week recovery period after the 1st dose).

With further dosing (Week 37), minimal to moderate focal retinal vacuolation was observed in 2 of 6 eyes from Group 3 males (0.3 mg/eye), 3 of 4 eyes from Group 4 males (1.0 mg/eye), 2 of 6 eyes from Group 5 males (3.0 mg/eye), 3 of 6 eyes from Group 6 males (3.0 mg/eye + Lucentis™), 4 of 6 eyes from Group 3 females, 2 of 4 eyes from Group 4 females, 5 of 6 eyes from Group 5 females, and 4 of 6 eyes from Group 6 females (Table 11). Mild to moderate diffuse retinal vacuolation was observed in 3 of 6 eyes from Group 5 males, 2 of 6 eyes from Group 6 males, and 2 of 6 eyes from Group 6 females.

At Week 41, following a 4-week recovery period, focal retinal vacuolation persisted in 4 of 4 eyes from Group 5 males and 3 of 4 eyes from Group 5 females (only ARC1905-treated group evaluated), but the severity had decreased (minimal to mild). As indicated in the rabbit study, the finding most likely reflects deposition of the PEGylated aptamer in the retinal cells.

At Week 37, unilateral or bilateral vacuolation (mild) of the optic tract in the brain was observed in 2 of 3 Group 5 males. This finding was reversible.

Table 12: Incidence of Microscopic Findings in the Eye – 1-Month and 9-Month Ocular Toxicity Study in Dogs

Week 1

Observations: Neo-Plastic and Non Neo-Plastic	MALES					FEMALES				
Removal Reason: Scheduled Euthanasia	0 mg/eye	0.3 mg/eye	1.0 mg/eye	3.0 mg/eye	3.0+ 0.5 mg/	0 mg/eye	0.3 mg/eye	1.0 mg/eye	3.0 mg/eye	3.0+ 0.5 mg/
Number of Animals on Study :	2	2	2	2	2	2	2	2	2	2
Number of Animals Completed:	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)
EYE (LEFT);										
Examined	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)
Within Normal Limits	2	2	2	0	1	2	2	1	0	1
Vacuolation; retinal; focal	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(1)	(2)	(1)
minimal	0	0	0	1	0	0	0	0	0	0
mild	0	0	0	0	0	0	0	1	0	0
moderate	0	0	0	1	0	0	0	0	2	1
Inflammation, Acute; anterior chamber	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	0	1	0	0	0	0	0
Inflammation, Acute; vitreous	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
moderate	0	0	0	0	1	0	0	0	0	0
EYE (RIGHT);										
Examined	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)
Within Normal Limits	2	2	1	0	0	2	1	2	0	0
Vacuolation; retinal; focal	(0)	(0)	(0)	(2)	(2)	(0)	(0)	(0)	(2)	(2)
minimal	0	0	0	0	1	0	0	0	1	2
mild	0	0	0	1	1	0	0	0	0	0
moderate	0	0	0	1	0	0	0	0	1	0
Atrophy; retinal; focal	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
mild	0	0	0	0	0	0	1	0	0	0
Inflammation, Acute; vitreous; conjunctiva	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
moderate	0	0	1	0	0	0	0	0	0	0
Inflammation, Acute; anterior chamber	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	1	0	0	0	0	0	0	0

Week 37

Observations: Neo-Plastic and Non Neo-Plastic	MALES						FEMALES					
Removal Reason: Scheduled Euthanasia	0 mg/eye	0 mg/eye	0.3 mg/eye	1.0 mg/eye	3.0 mg/eye	3.0+ 0.5 mg/	0 mg/eye	0 mg/eye	0.3 mg/eye	1.0 mg/eye	3.0 mg/eye	3.0+ 0.5 mg/
Number of Animals on Study :	3	2	3	2	3	3	2	2	3	2	3	3
Number of Animals Completed:	(3)	(2)	(3)	(2)	(3)	(3)	(2)	(2)	(3)	(2)	(3)	(3)
EPIDIDYMIS; (continued)												
Inflammation, Chronic; focal	(0)	(1)	(0)	(0)	(1)	(0)	(-)	(-)	(-)	(-)	(-)	(-)
minimal	0	1	0	0	1	0	-	-	-	-	-	-
ESOPHAGUS;												
Examined	(3)	(2)	(0)	(0)	(3)	(3)	(2)	(2)	(0)	(0)	(3)	(3)
Within Normal Limits	3	2	0	0	3	3	2	2	0	0	3	3
EYE (LEFT);												
Examined	(3)	(2)	(3)	(2)	(3)	(3)	(2)	(2)	(3)	(2)	(3)	(3)
Within Normal Limits	2	2	3	1	0	0	2	2	0	1	1	0
Vacuolation; retinal; diffuse	(0)	(0)	(0)	(0)	(1)	(1)	(0)	(0)	(0)	(0)	(0)	(1)
mild	0	0	0	0	0	1	0	0	0	0	0	0
moderate	0	0	0	0	1	0	0	0	0	0	0	1
Vacuolation; retinal; focal	(0)	(0)	(0)	(1)	(2)	(2)	(0)	(0)	(2)	(1)	(2)	(2)
minimal	0	0	0	1	2	0	0	0	1	1	1	1
mild	0	0	0	0	0	2	0	0	1	0	1	1
Atrophy; retinal; diffuse	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
marked	0	0	0	0	0	0	0	0	1	0	0	0
Atrophy; retinal; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	0	0	0	0	0	0	0	0
EYE (RIGHT);												
Examined	(3)	(2)	(3)	(2)	(3)	(3)	(2)	(2)	(3)	(2)	(3)	(3)
Within Normal Limits	3	2	1	0	1	1	2	2	1	1	0	0
Vacuolation; retinal; diffuse	(0)	(0)	(0)	(0)	(2)	(1)	(0)	(0)	(0)	(0)	(0)	(1)
mild	0	0	0	0	1	0	0	0	0	0	0	0
moderate	0	0	0	0	1	1	0	0	0	0	0	1
Vacuolation; retinal; focal	(0)	(0)	(2)	(2)	(0)	(1)	(0)	(0)	(2)	(1)	(3)	(2)
minimal	0	0	2	2	0	0	0	0	1	1	1	1
mild	0	0	0	0	0	1	0	0	1	0	1	0
moderate	0	0	0	0	0	0	0	0	0	0	1	1

Source: Excerpts from Histopathology Report Table 1
Note: *Table not included in initial nonclinical review filed for SDN-16.*

Because of the lack of a clear dose response and the findings not being uncommon after IVT injections, the Applicant considered the following findings most likely related to the injection procedure:

- At Week 1, acute inflammation (mild to moderate) in the vitreous, conjunctiva, and/or anterior chamber, characterized by infiltration with neutrophils and fibrin deposition, was observed in one eye each of one Group 4 male (# 4533)[1] and one Group 6 male (# 4561). This finding was not observed at Week 37.
- Focal retinal atrophy (mild), characterized by loss of cells from the inner nuclear layer and outer nuclear layer, was observed in one Group 3[2] female (# 4524) at Week 1. At Week 37, focal retinal atrophy (minimal) was observed in the left eye of one control male (Group 1) and diffuse retinal atrophy (marked) was observed in the left eye in one Group 3 female (# 4528).

Female # 4528 with diffuse retinal atrophy on Week 37 did not have any other histopathological findings. Retinal vacuolation was not present in this animal. Individual clinical observations showed a higher frequency of the following findings in the left eye in this female: bloodshot eye (starting on Day 76), eye abnormality (starting on Day 106; nature of the abnormality was not specified), excessive lacrimation (starting on Day 141), and eye enlarged (starting on Day 203). Ophthalmic observations showed the left eye was normal up to Week 9 (after 3 monthly IVT injections). Posterior synechia, hyphema, fibrin/pigment deposition onto the anterior lens capsule, and complete retinal detachment were noted on the next evaluation timepoint (Week 13 prior to dosing). The hyphema, fibrin/pigment deposition resolved in subsequent evaluations. As these findings could result from the IVT injection procedure and only one eye was affected, this reviewer agrees the findings are likely procedure related.

There were no test article-related findings in any systemic tissue.

Toxicokinetics (Following doses 1, 3, and 10 [Days 1, 57, and 253 [males]/255 [females], respectively] at 0.5, 3, 8, 24, 72, and 144 hours postdose)

ARC1905 was detected in the systemic circulation at all dose levels (mean values ≤488.7 ng/mL). The plasma concentration increased with dose but generally in a less than dose proportional manner. The T_{max} was observed between 8-24 hours. The plasma levels were sustained through 144 hours (7 days) after IVT injection, suggesting slow release from the eye. No consistent differences in mean ARC1905 plasma concentrations were apparent between Days 1 and 57 (after 1 and 3 doses, respectively). However, plasma concentrations were considerably higher (~2-40x) on Day 253/255 (after 10 doses) compared to a single or 3 doses at the mid and high dose. There were no significant differences between Groups 5 and 6 (i.e., with and without co-administration of Lucentis™), indicating that Lucentis™ had no influence on the uptake of ARC1905 into plasma.

[1] There is a mistake in the tabulated data, as this finding is attributed to one Group 3 male in the table instead of the Group 4 male.
[2] There is a mistake in the tabulated data, as this finding is attributed to one Group 2 female in the table instead of the Group 3 female.

Table 13: Mean ARC1905 Concentration in Plasma of Dogs (ng/mL) – Chronic Ocular Toxicity Study

Group Mean ARC1905 Concentration in Plasma of Dogs (ng/mL)

Group No.	Treatment	Time Post-Injection (hours)					
		0.5	3	8	24	72	144
Study Day 1							
1	Control	ND	BLQ	ND	ND	ND	ND
2	Control*	ND	BLQ	ND	ND	ND	ND
3	ARC1905, 0.3 mg/eye	25.6	32.0	30.9	12.0	5.0	BLQ
4	ARC1905, 1.0 mg/eye	34.2	25.0	48.1	34.1	15.3	7.7
5	ARC1905, 3.0 mg/eye	45.3	10.0	20.9	66.6	51.6	25.7
6	ARC1905, 3.0 mg/eye + 0.5 mg/eye Lucentis™	44.4	11.1	26.6	68.5	50.5	24.2

Group No.	Treatment	Time Post-Injection (hours)					
		0.5	3	8	24	72	144
Study Day 57 (Dose 3)							
1	Control	ND	BLQ	ND	ND	ND	ND
2	Control*	ND	BLQ	ND	ND	ND	ND
3	ARC1905, 0.3 mg/eye	12.8	23.8	17.3	7.4	5.4	2.8
4	ARC1905, 1.0 mg/eye	35.9	21.8	43.3	40.7	19.0	8.5
5	ARC1905, 3.0 mg/eye	46.9	8.7	24.6	60	44.9	26.4
6	ARC1905, 3.0 mg/eye + 0.5 mg/eye Lucentis™	38.6	8.1	22.5	82.6	48.8	29.3

Group No.	Treatment	Time Post-Injection (hours)					
		0.5	3	8	24	72	144
Study Day 253/255 (Dose 10)							
1	Control	ND	BLQ	ND	ND	ND	ND
2	Control*	ND	BLQ	ND	ND	ND	ND
3	ARC1905, 0.3 mg/eye	6.0	29.3	15.8	10.6	3.6	ND
4	ARC1905, 1.0 mg/eye	87.7	198.3	183.1	62.4	23.5	ND
5	ARC1905, 3.0 mg/eye	129.2	296.5	488.7	187.9	59.9	31.2
6	ARC1905, 3.0 mg/eye + 0.5 mg/eye Lucentis™	149.9	342.9	372.7	175.1	66.6	ND

ND - Not Determined BLQ – below the lower limit of quantification (3.4 ng/mL)

*Two injections (control for Group 6)

For groups and time points where some animals had measurable values and some were BLQ, the group mean was calculated by assigning a value of ½ of the LLOQ (1.7 ng/mL) for the BLQ samples.

Source: Study Report Section 10.10 Toxicokinetics

Dosing Solution Analysis

Samples from Doses 1, 5, and 10 were analyzed. The study report indicates that samples were within 2% of the nominal concentrations. However, only the dose formulation analysis protocol was included in Appendix 2 (i.e., no results). Values were confirmed from the draft report (SD # 9; submitted 2-18-2009).

Systemic Route Repeat-Dose Studies

7-Day IV Route Repeat-dose Studies

Repeat-dose toxicity studies of ARC1905 administered IV by bolus injection followed by continuous infusion for 7 consecutive days were conducted in Sprague-Dawley rats and Cynomolgus monkeys. These studies were reviewed under the initial IND (Chen & Rivera, filed in DARRTS on 9-26-2008). Key findings per the nonclinical review are listed below with additional comments by this reviewer in italics.

A Repeated-Dose Study in Sprague-Dawley Rats of the Toxicity, Toxicokinetics and Pharmacodynamics of ARC1905 Administered Intravenously by Bolus Injection followed by Continuous Infusion for 7 Consecutive Days with a 1 or 14-Day Recovery Period (Study No. 501280)

Doses: ARC1905 was administered to animals via IV bolus injection on Day 1 of 0 (saline), 26, 54 or 100 mg/kg in a volume of 20 mL/kg, followed by continuous IV infusion from Day 1 to Day 8 in a volume of 37.44 mL/kg/day at a rate of 0.026 mL/kg/min to provide aptamer infusion rates of 0, 0.034, 0.070 or 0.130 mg/kg/min and aptamer cumulative doses of 0, 367, 760 or 1410 mg/kg.
Number/sex/group or timepoint (main study): 6/sex/group

Key findings:

- Decreased RBC parameters and WBC and platelet counts, increased PT and APTT values, and decreased fibrinogen values were observed at all test article dose levels (≥ 367 mg/kg).
- Clinical chemistry examinations showed a slight increase in glucose and urea levels at the mid dose and high dose, and a dose-dependent decrease in cholesterol, triglyceride, total protein, and albumin levels at ≥ 367 mg/kg.
- Increased liver, popliteal lymph node, adrenal, and spleen weights and decreased thymus weight were seen at 367, 760, or 1410 mg/kg, which correlated to the histological findings.
- Histopathological findings included vacuolation, basophilia and/or hypertrophy/hyperplasia and/or infiltration of macrophages in multiple tissues, predominantly affecting the mononuclear phagocyte system.
    - *Minimal to slight or moderate vacuolated macrophages in the eyes (ciliary body, the iris and scleral or periscleral connective tissue) were observed at ≥ 367 mg/kg.*

- ARC1905 was associated with lymphoid atrophy and/or necrosis in thymus, and myeloid/erythroid hypocellularity in bone marrow at ≥760 mg/kg.
- Reversibility was noted in most changes except for macrophage hypertrophy/hyperplasia with vacuolation in histological examination.
- A NOAEL was not determined in this study.
- At 367 mg/kg, the exposure to ARC1905 ($AUC_{0\text{-}last}$) was 33355 µg•hr/mL and the C_{max} was 364 µg/mL

Based on C_{max} of 68.4 ng/mL and $AUC_{0\text{-}last}$ of 24 µg•hr/mL observed in humans, there is an exposure margin of >5000X (C_{max}) and >1300X (AUC) at the rat low dose of 367 mg/kg, which supports low concern for similar findings to be observed in humans.

Except for the thymus and bone marrow, where lymphoid atrophy/necrosis and hypocellularity, respectively, were noted, the presence of ARC1905 related vacuoles in tissue macrophages was not associated with evidence of degeneration or inflammation in tissue and parenchymal cells of organs.

A Repeated-Dose Study in Cynomolgus Monkeys of the Toxicity, Toxicokinetics, Pharmacodynamics, and Toxicodynamics of ARC1905 Administered Intravenously by Bolus Injection followed by Continuous Infusion for 7 Consecutive Days with a 1- or 14-Day Recovery Period (Study No. KSH00040)

Doses: ARC1905 was administered on Day 1 via IV bolus injection of 0 (saline control), 1, 3, 10, 30, and 100 mg/kg in a volume of 20 mL/kg, followed by continuous IV infusion ending on Day 8 in a volume of 37.44 mL/kg/day at a rate of 0.026 mL/kg/min to provide aptamer infusion rates of 0, 0.013, 0.039, or 0.13 mg/kg/min and aptamer total doses of 0, 141, 423, or 1410 mg/kg.
Number/sex/group or time point (main study): 3

Key findings:

- Mortalities occurred at the high dose (1410 mg/kg) and were attributed to cardiopulmonary failure resulting from hemorrhage and edema in the heart (myocardium) and lungs.
- Other adverse effects included anticoagulation, anemia, thrombocytopenia, hypoproteinemia, and increased incidence of rouleaux formation. The decrease in hemoglobin and increased incidence of rouleaux formation were observed at all dose levels. APTT was prolonged at ≥423 mg/kg and PT at 1410 mg/kg.
- Organ weight changes included increased liver, spleen, adrenal, and kidney at ≥141 mg/kg, popliteal lymph nodes at ≥424 mg/kg, and lung and heart at 1410 mg/kg.
- All animals had one or more of the following findings: basophilic granules, basophilic swirled material, and basophilic vacuolization of macrophages in almost every tissue. The incidence, severity (minimal to marked), and distribution were dose dependent.

- Most findings were reversible or partially reversible, except for vacuolation in macrophages still present in multiple tissues.
- ARC1905 was not associated with activation of complement, as assessed by plasma C3a and Bb values.
- A NOAEL was not identified.
- At 141 mg/kg (lowest dose), the exposure to ARC1905 ($AUC_{0\text{-last}}$) was 12968-14370 µg•hr/mL and the C_{max} was 165-179 µg/mL.
- The low dose of 141 mg/kg was identified as a pharmacologically active dose and provided ≥ 99% inhibition of complement activity (ATCF) through 0.5 hours after the start of infusion.

Based on C_{max} of 68.4 ng/mL and AUC0-last of 24 µg•hr/mL observed in humans, there is an exposure margin of >2000X (C_{max}) and 540X (AUC) at the monkey low dose of 141 mg/kg. Therefore, it is considered unlikely that systemic tissue vacuolization and other adverse effects identified in the 7-day continuous IV dose study in monkeys will occur at the systemic exposures expected to be observed in humans.

At 141 mg/kg, the apparent accumulation of ARC1905-related material within tissue macrophages was not associated with evidence of degeneration, necrosis, or inflammation in the affected tissues. At 1410 mg/kg, ARC1905-related hemorrhage and edema was also present in many of the tissues where accumulation of ARC1905-related material in macrophages was observed but it is not known if the presence of large numbers of these macrophages was related to the presence of hemorrhage and edema.

7 Genetic Toxicology

The bacterial mutation assay and in vitro mammalian chromosomal aberration assays were reviewed under the initial IND (Chen & Rivera, filed in DARRTS on 9-26-2008). The following are excerpts of the Initial IND nonclinical review.

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study Title: Bacterial Reverse Mutation Assay of ACRC1905 (Study No. AB12SY.503. (b) (4))

Strains/species/cell line: *S. typhimurium* TA98, TA100, TA1535, and TA1537, and *E. coli* WP2uvrA
Doses used in definitive study: 50, 150, 500, 1500, and 5000 µg/plate ± S9 fraction (actual concentrations of 48.8, 148.8, 496.3, 1226.3 and 4712.5 µg/plate)

Key findings:

- ACR1905 did not increase the number of revertants compared to controls.
- Cytotoxicity or precipitation was not observed.

7.2 *In Vitro* Assays in Mammalian Cells

Study Title: *In Vitro* Mammalian Chromosome Aberration Test of ACR1905 (Study No. AB12SY.341.(b) (4))

Strains/species/cell line: Human peripheral blood lymphocytes (HPBL)
Doses used in definitive study: 125, 250, 500, 1000, 1200, 1350 and 1500 μg/mL (actual concentrations of 135, 235, 451, 889, 1050, 1190, and 1300 μg/mL)
Concentrations selected for the evaluation of chromosomal aberrations were 500 and 250 μg/mL [≤ 11% reduction in mitotic index (MI)] and 1200 μg/mL (MI reduction from 53%-56%)

Key findings:

- ACR1905 did not increase the number of chromosomal aberrations compared to controls.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: Mouse Bone Marrow Erythrocyte Micronucleus Test with ARC1905 Given by Intravenous Injection

Study no:	AC10VW.123(b) (4)
Study report location:	DocuBridge Module 4.2.3.3.2 \\CDSESUB1\EVSPROD\nda217225\0004\m4\42-stud-rep\423-tox\4233-genotox\42332-in-vivo\ac10vw-123-(b) (4)\ac10vw-123-(b) (4).pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 14, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ARC1905, lot # X01B07001N,

Key Study Findings

- A single IV injection of ARC1905 at total aptamer doses up to 2000 mg/kg (376 mg/kg oligonucleotide content) did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in bone marrow of male and female mice.

- ARC1905 was negative in the mouse micronucleus assay, under the conditions of the assay.

Methods

Doses in definitive study:	ARC1905 (total aptamer) at 0 (vehicle), 500, 1000, or 2000 mg/kg (0, 94, 188 or 376 mg/kg of the oligonucleotide content, respectively)
Frequency of dosing:	Single dose
Route of administration:	IV injection
Dose volume:	12.53 mL/kg
Formulation/Vehicle:	PBS
Species/Strain:	ICR mice
Number/Sex/Group:	5/sex/group – euthanized at 24 hours postdose 5/sex/group in vehicle control and high dose – euthanized at 48 hours postdose
Satellite groups:	An additional high dose group (5/sex) to be used as replacement animals in the event of mortality
Basis of dose selection:	3-Day dose-range finding study - ARC1905 doses of 0 (vehicle), 500, 1000, 1500 or 2000 mg/kg based on the total aptamer (0, 94, 188, 282, or 376 mg/kg of the oligonucleotide content of ARC1905, respectively) – No mortalities, no significant changes in body weight, piloerection at all doses in males; the high dose for definitive assay was set at 2000 mg/kg (376 mg/kg of oligonucleotide)
Negative control:	Vehicle (PBS)
Positive control:	Cyclophosphamide monohydrate (CP), 50 mg/kg, 10 mL/kg

Study Validity

The study was found valid according to regulatory standards. The results for the negative controls were within the range for historical laboratory values the positive control article, induced a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes ($p \leq 0.05$, Kastenbaum-Bowman Tables). Dose formulation analysis showed results within specifications (96.0 to 97.2% of nominal).

Results

- A single IV injection of ARC1905 at doses up to and including 2000 mg/kg of the total aptamer (376 mg/kg oligonucleotide content) did not cause mortality or life-threatening clinical signs in male and female mice. Piloerection was observed at all doses in all males.

- No appreciable reductions in the ratio of polychromatic erythrocytes to total erythrocytes were observed in the test article-treated groups, relative to the respective vehicle control groups at 24 hours or 48 hours postdose.
- No statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in test article-treated groups, relative to the respective vehicle control groups, was observed in male or female mice at 24 hours or 48 hours postdose.

8 Carcinogenicity

No studies were conducted. The Applicant submitted a justification to support a waiver request not to conduct the carcinogenicity studies (NDA Module 1.12.13). The Applicant discussed their plan at the Type C meeting held on September 8, 2021. The Division had no objection to the Applicant's proposal to submit a waiver request.

The Applicant justification to omit the conduct of nonclinical carcinogenicity studies is based on avacincaptad pegol mechanism of action, route of administration, a supportive literature review, an analysis of pharmacological class effects, and nonclinical and clinical data collected to date. Some excerpts of the Applicant's justification are shown below. Reviewer's comments are presented in italics.

1. Mechanism of Action

Avacincaptad pegol's mechanism of action is independent of nuclear or hormone receptor binding, interaction with genetic material, perturbation of hormones, or other cellular pathways known to be involved in human cancer development. Additionally, a review of published literature and an accumulation of experience with the C5 inhibitor drug class (e.g., eculizumab, ravulizumab, avacopan) demonstrated that the effects of antagonism of C5 do not raise concerns about carcinogenicity.

> ***Reviewer's comments:*** *Per FDA approved label information, carcinogenicity studies (and genetic toxicity studies, as expected for monoclonal antibodies) were not conducted for the C5 inhibitors eculizumab and ravulizumab. Avacopan, a small molecule C5 receptor antagonist, was not carcinogenic in rats and hamsters at oral doses up to 100 mg/kg/day and was negative in the standard battery of genetic toxicity studies.*

Avacincaptad pegol is expected to be catabolized by endonucleases and exonucleases to oligonucleotides of shorter lengths. There is no evidence that avacincaptad pegol's metabolites or degradants are incorporated into nucleic acids that have potential for mutagenic activity. This position is also supported by the absence of genetic toxicity in the standard genotoxicity studies. In addition, avacincaptad pegol is administered via IVT injection, resulting in low systemic exposure.

The Applicant considered theoretical mechanisms by which avacincaptad pegol could affect carcinogenesis, including cancer progression related to alterations in C5 signaling and immune response through the mode of action of avacincaptad pegol. However, the Applicant considers such supposition as unlikely, based on the discussion presented in this waiver.

2. Published Literature Search

No additional safety signals for avacincaptad pegol were identified, beyond the information established through the clinical development program.

3. Systemic Exposure and Route of Administration

Following IVT administration, plasma levels of avacincaptad pegol (levels in the nanogram/mL range) were several orders of magnitude lower than those measured after intravenous (IV) administration of avacincaptad pegol (levels in the high microgram/mL range) in Sprague-Dawley rats and cynomolgus monkeys.

In the clinical setting, these results were also demonstrated in the Phase 1 OPH2000 study, where patients with neovascular AMD treated with avacincaptad pegol had plasma levels C_{max} in the nanogram/mL range; 68.4 ng/mL after the 2 mg IVT dose and 97.3 ng/mL after the 3 mg IVT dose. Mean trough plasma levels measured before the second dose at Week 4 and third dose at Week 8 were 20 ng/mL after the 2 mg IVT dose. These levels are several orders of magnitude lower than what was measured following IV administration of avacincaptad pegol (levels in the high microgram/mL range) given systemically. In Phase 1 Study OPH2000, there were no dose limiting toxicities at any dose level during the study and no particular safety concerns were identified. Systemic adverse events (AEs) were not frequently reported and only headache (8%), bronchitis (7%) and nausea (5%) were reported by three or more patients. No systemic AEs were assessed as related to avacincaptad pegol.

These product attributes, along with the well-documented negligible systemic exposure after IVT injection and intermittent dosing schedule indicate that there is limited potential for avacincaptad pegol to elicit systemic pharmacologic effects or toxicity at the recommended clinical dose regimen.

Reviewer's comments: *No adverse systemic findings were observed in the chronic IVT toxicity studies in rabbits and dogs up to the highest dose evaluated. The C_{max} at end of study in the high dose in rabbits was 43.3 ng/mL and that in the dogs was 488.7 ng/mL. Compared to the observed human exposure of 68.4 ng/mL at the recommended human dose, exposure margins are 0.63X in the rabbit and 7X in the dog. The mean systemic exposure in the rabbit was lower than that observed in the clinic and is not considered to provide support for systemic safety (see Section 8 below). The dog data provides support for the systemic safety of the proposed clinical dosing regimen.*

4. Discussion of Human Plasma Levels After Intravitreal Injection

In Phase 1 Study OPH2000, PK data were analyzed following multiple doses for 3 patients at 0.03 mg, 19 patients at 0.3 mg, 16 patients at 1 mg, 15 patients at 2 mg, and seven patients at 3 mg doses, respectively (Table 13). All available plasma concentration data after the first dose up to Week 4 were included in the PK data analysis for area under curve (AUC) determinations.

Table 14: Summary of Clinical Pharmacokinetic Parameters Following Multiple Intravitreous Injections of 0.03, 0.3, 1, 2, or 3 mg of Avacincaptad Pegol

	0.3 mg (N=19)		1 mg (N=16)		2 mg (N=15)		3 mg (N=7)	
Parameter	**Mean**	**%CV**	**Mean**	**%CV**	**Mean**	**%CV**	**Mean**	**%CV**
C_{max} (ng/mL)	21.9	35.9	73.1	34.4	68.4	57.8	97.3	75
t_{max} (days)	5.8	41.7	5.3	38.8	5.7	46.1	6.9	30.8
AUC_{0-t}	233	69.4	1164.1	29	999.9	71.9	1643.4	96.5
$AUC_{0-\infty}$	518.5	26.4	1589	34.2	1948.4	27.9	3349.6	72.6
$t_{½}$ (days)	13.7	26.2	13.5	47.7	15.5	43.5	14.5	36.1

Source: OPH2000 PK Report

Abbreviations: AUC0-∞ = area under the concentration-time curve to infinity; AUC0-t = area under the concentration-time curve from Time 0 to the last quantifiable time-point; C_{max} = maximum plasma concentration; CV = coefficient of variation; $t_{1/2}$ = time to half concentration (half-time); t_{max} = time to maximum concentration.

Note: Avacincaptad pegol plasma concentrations were not detectable in any patients receiving 0.03 mg doses.

Applicant's Table 1, Carcinogenicity Waiver

Mean maximum plasma concentrations were reached approximately 5 to 7 days after IVT injection, reflecting slow egress of avacincaptad pegol from the eye following injection.

The mean terminal $t_{1/2}$ values ranged from 13.5 to 15.5 days, most likely reflecting the long retention of avacincaptad pegol in the eye prior to entrance into and clearance from the blood compartment.

There was no meaningful accumulation of avacincaptad pegol in plasma following repeated dosing every 4 weeks (based on the pre-dose concentrations [C_{min}] prior to second and third dose on Week 4 and 8, respectively).

In summary, the product attributes, combined with the well-documented negligible systemic exposure after IVT injection and intermittent dosing schedule, indicate that there is limited potential for avacincaptad pegol to elicit systemic pharmacologic and carcinogenic effects at the recommended clinical dosage regimen.

Reviewer's comments: *In general, the Applicant is making the point that plasma concentrations in the clinic were low following IVT doses up to 3 mg and there was no accumulation with repeated dosing.*

5. Summary of Nonclinical Data

The nonclinical studies conducted to date (Module 4), indicate no findings suggestive of the potential for an increase in tumor formation, neoplastic transformation, or proliferative lesion.

Data from toxicology studies were also evaluated for signs of immunotoxic potential. Intravitreal toxicity studies showed no signs of immunosuppression, and nearly all changes and toxicity observations were confined to the eyes.

Toxicity studies with IV injection, in which the systemic exposure of avacincaptad pegol was several orders of magnitude higher than that measured in animals following IVT injection, showed lack of consistency in hematological changes or alterations in immune system organ weight. Additionally, there were no signs of increased infections or increased occurrence of tumors. The observed changes in clinical pathology parameters, namely decrease in reticulocytes and monocytes and increase in lymphocytes at ≥86.2 mg/kg, are likely reflective of hemodilution due to the circulating PEG from the aptamer.

Overall, the data obtained relating to plasma concentrations of avacincaptad pegol following IVT administration in New Zealand White rabbits and beagle dogs confirm that systemic exposure is extremely low (levels in the nanogram/mL range) relative to the plasma levels associated with systemic adverse effects in IV studies (levels in the high microgram/mL range). Hence, the systemic exposure associated with the clinical range of IVT doses would be expected to be similarly very low.

Reviewer's comments: *In the 7-day IV toxicity studies, there were some findings that could suggest immunosuppression. In rats, decreased WBC counts associated with myeloid/erythroid hypocellularity and lower thymus weights associated with lymphoid atrophy and/or necrosis were observed at ≥ 760 mg/kg. Both tissues had macrophage vacuolation. It is not clear then if the findings were secondary to the vacuolation or a direct effect of the aptamer. In the monkey, decreased neutrophil (40-78%), WBC (39-68%), and lymphocyte counts (39-57%) were observed at the high dose (1410 mg/kg). The findings were reversible or partially reversible during a 14-day recovery period.*

Nevertheless, the doses at which these findings were observed are substantially higher than the recommended human dose (2 mg) supporting minimal clinical concern for systemic immunosuppression (see exposure margins in Table 14 below).

On the other hand, as the IV studies were short term, the Applicant should not refer to these studies as relevant to assess tumor development.

6. Genotoxicity Studies

A lack of carcinogenicity potential of avacincaptad pegol is suggested based on the negative results from a battery of genotoxicity studies conducted. These studies indicated no mutagenic or clastogenic activity, and an absence of genetic toxicity signal.

7. Summary of Clinical Data

The results of the clinical studies conducted to date indicate no cause for carcinogenicity concern as there is no evidence suggestive of immunotoxicity or proliferative lesions.

Reviewer's comments: *Refer to clinical review for further details regarding this statement.*

8. Relationship of Nonclinical to Clinical Data

The NOAELs established in the avacincaptad pegol toxicology and safety pharmacology studies per the Applicant conclusions are provided in Table 14. This table also presents safety margins estimated using systemic exposures calculated for the animal studies compared to human exposures; C_{max} is used as an estimate of the safety margin where AUC was not calculated. The human systemic exposures used in these calculations included the mean area under the concentration-time curve from Time 0 to the last quantifiable time-point (AUC_{0-t}) and C_{max} values from patients treated with the recommended clinical dose of 2 mg once monthly (AUC_{0-t} = 999.9 ng•day/mL, C_{max} = 68.4 ng/mL; OPH2000 PK Report). Edits by this reviewer are shown in bold red.

Table 15: Systemic Exposure Margins from Toxicology Studies (IV and IVT)

Species	Duration and route of administration	Dose at NOAEL	C_{max} at NOAEL	$AUC_{0\text{-last}}$ (µg•hr/mL) at NOAEL	Margin to human $AUC_{0\text{-t}}$ at 2 mg once monthly[a]	Margin to human C_{max} at 2 mg once monthly[b]	Report
New Zealand White rabbits	IVT; One month (single dose); 9 months (10 injections, repeat-dose)	≥ 1.5 mg[c] **3.0 mg**	51.3 ng/mL **43.3 ng/mL (after 10 injections)**	Not calculated	-	≥ 0.75 **≥0.63**	XGL00005
Beagle dogs	IVT; One month (single dose); 9 months (10 injections, repeat-dose)	1.0 mg[c] **3.0 mg**	198.3 ng/mL **489 ng/mL (after 10 injections)**	Not calculated	-	2.9 **≥7**	XGL00006
Sprague-Dawley rats	Single IV bolus injection	260 mg/kg **26 mg/kg**	M: 2465 µg/mL F: 2205 µg/mL **M: 364 µg/mL** **F: 397 µg/mL**	M: 18574 F: 17279 **M: 2658** **F: 1933**	> 720 **>80**	-	KSH00038
	Single IV bolus injection followed by continuous IV infusion over 7 consecutive days	Not identified; data is provided for the lowest dose tested (367 mg/kg)	364 µg/mL	33355	1390	-	501280
Pregnant Sprague-Dawley rats	IV bolus injection; 12 days	1.2 mg/kg	C_0 = 26.5 µg/mL (GD6) **C_0 = 26.5 µg/mL (GD17)**	128 (GD6) **131 (GD17)**	~~64~~[d] **5.3** **5.5**	387 **376**	20334075

Pregnant New Zealand White rabbits	IV bolus injection; 13 days	1.2 mg/kg	C_0 = 41.7 µg/mL (GD7) **C_0 = 35.7 µg/mL (GD19)**	78.8 (GD7) **81.3 (GD19)**	~~42.7~~[e] **3.3** **3.4**	610 **522**	20332454

Continuation Table 14: Systemic Exposure Margins from Toxicology Studies (IV and IVT)

Species	Duration and route of administration	Dose at NOAEL	C_{max} at NOAEL	$AUC_{0\text{-last}}$ (µg•hr/mL) at NOAEL	Margin to human $AUC_{0\text{-t}}$ at 2 mg once monthly[a]	Margin to human C_{max} at 2 mg once monthly[b]	Report
Cynomolgus monkeys	Single IV bolus injection followed by continuous IV infusion over 24 hours	28.7 mg/kg	M: 215 µg/mL F: 202 µg/mL	M: 3569 F: 3869	> 149	-	KSH00033
	Single IV bolus injection followed by continuous IV infusion over 7 consecutive days	Not identified; data is provided for the lowest dose tested (141 mg/kg)	M: 165 µg/mL F: 179 µg/mL	M: 12968 F: 14370	> 540	-	KSH00040
	Single IV injection	10 mg/kg	220 µg/mL	2238	93	-	KSH00039

Abbreviations: $AUC_{0\text{-last}}$= area under the concentration- time curve to the last quantifiable time-point; $AUC_{0\text{-t}}$= area under the concentration- time curve from Time 0 to the last quantifiable time-point; C_0 = back-extrapolated concentration at time 0; C_{max}=peak plasma concentration; F = females; GD = gestational day; IV=intravenous; IVT=intravitreal; M = Males; NOAEL = no observed adverse effect level.

[a]: The human $AUC_{0\text{-t}}$ value at 2 mg once monthly was 999.9 ng•day/mL (23.998 µg•hr/mL)(OPH2000 PK Report).

[b]: The human C_{max} value at 2 mg once monthly was 68.4 ng/mL (OPH2000 PK Report).

[c]: Avacincaptad pegol was administered to both eyes of the animals.

[d]: For the calculation of the margin to human $AUC_{0\text{-t}}$, the cumulative exposure ($AUC_{0\text{-last}}$) over the dosing period of 12 days was used.

[e]: For the calculation of the margin to human $AUC_{0\text{-t}}$, the cumulative exposure ($AUC_{0\text{-last}}$) over the dosing period of 13 days was used.

Applicant Table 2, Carcinogenicity Waiver Request

Reviewer's comments: *This reviewer agrees with the NOAEL except for those corrected in red. Because long-term studies are the ones with primary relevance for carcinogenicity studies, as noted under item 3 above, compared to the observed human exposure of 68.4 ng/mL at the recommended human dose, exposure margins are 0.63X in the rabbit and 7X in the dog based on plasma exposure observed at the end of the 9-month studies. The mean systemic exposure in the rabbit was lower than that observed in the clinic and is not considered to provide support for systemic safety.*

9. Practicality of Conducting Long-Term Carcinogenicity Studies with Avacincaptad Pegol

Reviewer's comments: *The Applicant provided some reasons why carcinogenicity studies by the IVT route in rodents may not be technically feasible (i.e., IVT injections in rodents produce cumulative inflammatory changes in eyes, which would likely obscure the evaluation of neoplastic changes; the proposed maximum feasible dose by long-term, repeat IVT injection would be limited based on ophthalmic anatomy in rodents). This reviewer agrees these are reasonable limitations.*

The Applicant also addressed the issue of IV administration would result in excessive systemic exposure but nominal exposure to the eye. However, this reviewer believes that if studies were needed, the IV route will be an appropriate route to conduct these studies. The Applicant also indicated that monkeys are not an appropriate model for evaluation of carcinogenic risk as their lifespan in captivity exceeds 20 years.

Lastly, based on the negligible systemic exposure and lack of cause for concern, the Applicant considers that carcinogenicity studies with avacincaptad pegol are not warranted. See "Conclusion" below for this reviewer's assessment.

10. Pharmacological Class Consideration

Reviewer's comments: *The Applicant indicated that relevant data for three FDA-approved products with similar pharmacology were assessed, namely Soliris® (eculizumab; recombinant humanized monoclonal immunoglobulin G (IgG)2/4 antibody targeting inhibition of C5 cleavage; approved 2007), Ultomiris® (ravulizumab; humanized monoclonal antibody; approved 2018), and Tavneos® (avacopan; small molecule C5a receptor antagonist; approved 2021). These products are for systemic administration (IV, SC or oral). The Applicant also searched for relevant data for Macugen (pegaptanib, an IVT administered pegylated oligonucleotide aptamer although directed against VEGF; approved 2004). To date, the Applicant is unaware of any association with the use of these*

products and carcinogenicity risk since their U.S. marketing authorization. The assessment included a 10-year pharmacovigilance analysis of eculizumab.

As noted above, carcinogenicity studies in rats and hamsters were conducted for avacopan and no tumorigenic potential was observed at oral doses 3X and 6X higher, respectively, than the MRHD for the oral indication (Tavneos Prescribing Information, 2021).

Reviewer Conclusions on the Need of Carcinogenicity Assessment: The Applicant considers that avacincaptad pegol is not expected to be carcinogenic in humans and as such no nonclinical carcinogenicity studies are required to support the initial NDA for the proposed indication, treatment of GA secondary to AMD.

The Applicant proposed the following language for Section 13.1 “Carcinogenesis, Mutagenesis, and Impairment of Fertility” of the label:

- No studies have been conducted on the carcinogenic potential of avacincaptad pegol.
- Avacincaptad pegol was negative in in vitro (bacterial reverse mutation assay, chromosomal aberration in mammalian cells) and in vivo (mouse bone marrow micronucleus) assays.

This reviewer considers that based on the low systemic exposure observed after IVT administration at the recommended clinical dose, toxicology as well as clinical data showing no reasons for concern, and marketing experience with molecules with a similar pharmacological target or structure, the conduct of the carcinogenicity studies is not warranted. The proposed label language is in principle considered acceptable (see separate label review for recommended edits).

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

The Applicant is requesting a waiver for the conduct of specific nonclinical developmental and reproductive toxicity (DART) studies for avacincaptad pegol (NDA Module 1.12.13). The Applicant considers that fertility and early embryonic development (FEED) and pre- and postnatal development (PPND) studies are not required for the proposed indication of treatment of GA secondary to AMD.

The topic of nonclinical DART studies was discussed at a Type C meeting held on September 8, 2021 (Type C Meeting Minutes, dated September 21, 2021) and in accordance with the advice received, the Applicant submitted a waiver request for FEED and PPND studies.

The Applicant believes the low amount of avacincaptad pegol that is systemically absorbed is not expected to be absorbed by reproductive tissues. As such, avacincaptad pegol administered by IVT injection, once monthly, is not expected to be associated with any measurable exposure to gonadal or embryo/fetal tissues in humans, which reduces the concern about effects on reproductive function. The Applicant concluded that overall, the extensive nonclinical toxicity and drug exposure data from single and chronic IVT, and subacute IV studies, as well as data from the EFD studies demonstrated no potential for reproductive or developmental toxicity in humans.

Some excerpts of the Applicant's justification are shown below. Reviewer's comments are presented in italics.

1. Target Patient Population/Therapeutic Indication Considerations

The proposed patient population and therapeutic indication for avacincaptad pegol includes patients with GA secondary to AMD. Overall, AMD typically manifests at ≥ 50 years of age. The target population of avacincaptad pegol is generally not reproductively capable, as the mean age of natural menopause in women varies from 42-53 years. In addition to the limited number of reproductively capable patients that may be therapeutic candidates for avacincaptad pegol, the potential developmental and reproductive risk of avacincaptad pegol is further reduced by its biochemical nature, route of administration, and limited systemic exposure.

2. Systemic Exposure and Route of Administration

Reviewer's comments: *The Applicant provided the same justification as that under the same topic (Item no. 3) to support the carcinogenicity waiver request (see this review Section 8 Carcinogenicity).*

No adverse effects were observed in reproductive organs in the chronic IVT toxicity studies in rabbits and dogs up to the highest dose evaluated. The C_{max} at end of study in the high dose in rabbits was 43.3 ng/mL and that in the dogs was 488.7 ng/mL. Compared to the observed human exposure of 68.4 ng/mL at the recommended human dose, exposure margins are 0.63X in the rabbit and 7X in the dog. The mean systemic exposure in the rabbit was lower than that observed in the clinic and is not considered to provide support for systemic safety.

However, as noted in Table 14 under Section 8. Carcinogenicity of this review, the NOAEL from the 7-day IV studies provide exposure margins >1390X (rat) and >540-fold in the monkey based on AUC, supporting the Applicant's conclusion that the low levels after IVT injection in humans are not expected to cause effects in the reproductive organs.

3. Pharmacology Considerations

The Applicant considered relevant information for the three FDA-approved products, Soliris® (eculizumab), Ultomiris® (ravulizumab), and Tavneos® (avacopan), with a similar pharmacology and known effects of target engagement. Macugen® (pegaptanib) was also included in this assessment as it has similar physicochemical properties to avacincaptad pegol and is the only other approved RNA-based aptamer.

Soliris (eculizumab) - recombinant humanized monoclonal IgG2/4 antibody targeting inhibition of C5 cleavage – IV administration

The Applicant cited reports from the published literature with the following conclusions:

- Therapeutic doses of eculizumab to treat paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, and preeclampsia did not affect the complement system of newborn (reference provided).
- In a 10-year pharmacovigilance analysis of eculizumab, 434 women exposed to eculizumab during pregnancy showed a comparable rate of live births and a low rate of maternal complications when compared to nontreated patients. Additionally, no teratogenic effects in fetuses were observed during the ten-year period (reference provided).
- Based on the literature, C5 inhibition during pregnancy appears unlikely to cause adverse effects in pregnant mothers or infants. In fact, targeting C5 inhibition in a pregnant woman is considered an effective therapeutic strategy for various disease states including preeclampsia and anti-phospholipid syndrome (references provided).

Ultomiris (ravulizumab) - humanized monoclonal antibody designed to bind to and prevent the activation of C5 – IV administration

To date, the Applicant is unaware of any association with the clinical use of ravulizumab and developmental and reproductive toxicity risk in humans since its U.S. marketing authorization in 2018.

Tavneos (avacopan) - C5a receptor antagonist – Oral administration

Of the embryo-fetal developmental (EFD) studies conducted with avacopan, oral administration to rabbits and hamsters showed no evidence of fetal harm. Maternal toxicity, evidenced by decreased body weight gains, was observed only in pregnant rabbits (Tavneos Prescribing Information).

In an EFD study in hamsters, an increase in a skeletal variation described as supernumerary ribs was noted in avacopan-treated hamsters at the dose of 1000 mg/kg/day. This finding was considered to be a developmental delay as supernumerary ribs can resolve into the vertebral arch later in development. Although there was an

apparent avacopan treatment-related increase for this finding in this EFD study, the variation was not judged to be adverse (would not be expected to affect long-term survival). To date, the Applicant is unaware of any association with the clinical use of avacopan and developmental or reproductive risk in humans since its U.S. marketing authorization in 2021.

Reviewer's comments: *The Applicant noted that like avacopan, an EFD study in pregnant rats dosed with IV avacincaptad pegol resulted in a similar skeletal variation of increased incidence of supernumerary ribs (short), which are similarly anticipated to resolve later in development. Therefore, the Applicant proposes to include a description of the skeletal variation, in Section 8.1 of the proposed label, considering the language in the regulatory precedent (Tavneos Prescribing Information).*

(b) (4)

Macugen (pegaptanib) – anti-VEGF PEG aptamer – IVT administration

Of the EFD studies conducted with pegaptanib, IVT and IV administration to rabbits and mice showed no developmental toxicity or other toxicologically significant findings, respectively at relevant human exposure. Additionally, pegaptanib has been marketed in the U.S. since 2004 and has not been demonstrated to be associated with any developmental or reproductive toxicity.

The Applicant believes that specific DART studies conducted with avacincaptad pegol would not provide information beyond what is already known from the drug products with similar pharmacology or structure as discussed above, and that, in the rare case where an AMD patient is capable of reproduction, it is anticipated that the limited systemic C5 inhibition from avacincaptad pegol would not result in reproductive or developmental toxicities or any related adverse effects.

4. Toxicity and Toxicokinetic Considerations

Across the pivotal nonclinical single-dose and repeated-dose toxicity studies, no avacincaptad pegol-related effects on absolute or relative reproductive organ (ovaries, uterus, epididymis, testes, and prostate gland) weights were identified.

Reviewer's comments *– See reviewer's comments under Item 2 above. In the 7-day IV toxicity studies in rats and monkeys, vacuolated macrophages were observed in almost every tissue examined. In the rat, the finding was observed in the ovaries, oviduct, uterus, vagina, epididymis, testes, prostate, and mammary glands at all dose levels (≥367 mg/kg), and it was of minimal to moderate*

severity. In the monkey, macrophage vacuolation was observed in the vagina, cervix, oviduct, and testes only at the high dose (1410 mg/kg) and it was of minimal to mild severity. The vacuolated macrophages were not associated with evidence of degeneration or inflammation in the reproductive organs and therefore, the finding was not considered adverse. Vacuolation was not observed in any systemic tissue in the ocular toxicity studies. The overall data support minimal concern for systemic tissue vacuolation at the intended IVT dosing regimen.

5. Summary of Embryo-Fetal Developmental Studies

Rat EFD study - Administration of avacincaptad pegol by once daily IV bolus injection between gestational day (GD) 6 and GD17 was well tolerated in pregnant Sprague-Dawley female rats at levels of 0, 0.1, 0.4, and 1.2 mg/kg/day. A non-adverse avacincaptad pegol-related variation of short thoracolumbar supernumerary rib (also defined as an ossification site without distal cartilage) as described for avacopan was observed which occurred in a dose-dependent manner. There was no impact considered adverse on any maternal or fetal parameter. Based on these results, the maternal and fetal no observed adverse effect level (NOAEL) was considered to be 1.2 mg/kg/day.

Rabbit EFD study – Administration of avacincaptad pegol by once daily IV bolus injection between GD7 and GD19 was well tolerated in New Zealand White pregnant rabbits at levels of 0, 0.12, 0.4, and 1.2 mg/kg/day. There were no avacincaptad pegol-related impact on any measured maternal or fetal parameter. Based on these results, the maternal and fetal NOAEL was considered to be 1.2 mg/kg/day.

Reviewer's comments: *As noted above, increased incidence of the finding of full thoracolumbar supernumerary ribs was observed in rabbits at the high dose. The increase was slightly above concurrent or historical control range.*

No adverse effects on maternal well-being or c-section parameters were observed up to a dose of 1.2 mg/kg/day (highest dose) in both rabbit and rat EFD studies. The NOAEL for maternal toxicity was the high dose in each study. Based on C_{max} value at end of study, the rabbit NOAEL provides exposure margins of 522X (rabbit) and 376X (rats) the observed human plasma levels of 68.4 ng/mL. Based on $AUC_{0\text{-}last}$, the exposure margins are 3.3X (rabbit) and 5.3X (rat), the human AUC of 24 µg•hr/mL.

Reviewer Conclusions on the Need of Fertility and Early Embryonic Development (FEED) and Pre- and Postnatal Development (PPND) Studies

This reviewer agrees the weight of evidence supports that the studies can be omitted particularly based on nonclinical data showing (1) lack of adverse effects in reproductive organs in the 9-month IVT toxicity study in dogs (rabbit systemic exposure was not high enough in the 9-month IVT toxicity study to support safety), (2) lack of

adverse effects in reproductive organs in the 7-day IV toxicity studies in rats and monkeys at AUCs over 500X that observed in the clinical trials and (3) lack of adverse effects on maternal well-being, c-section parameters or embryofetal development in the EFD studies in rats and rabbits at AUC 5.5X and 3.4X higher than that observed in the clinical trials, respectively (See Tables 14 and 20 of this review for exposure margins).

9.2 Embryofetal Development

Study title: An Embryo-Fetal Development Study of Zimura Given by Intravenous Injection in Rabbits

Study no.:	20332454
Study report location:	DocuBridge Module 4.2.3.5.2 \\CDSESUB1\EVSPROD\nda217225\0004\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42352-embryo-fetal-dev\20332454\20332454.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 26, 2022
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ARC1905, Zimura™ (Avacincaptad Pegol Sodium) Injection (oligonucleotide content: 19.9 mg/mL), batch/lot # 3-FIN-4019, ≥85.0% pure AX-HPLC), ≥90.0% pure (IP-HPLC)

Key Study Findings

- There were no adverse findings on any maternal or fetal parameter.
- Compared to controls, there was an increased incidence of full thoracolumbar supernumerary ribs at the high dose. The increase was slightly above the concurrent control and historical control range. Considering the high spontaneous variability of this finding in rabbits and the lack of any other signs of developmental toxicity, the finding is not considered adverse.
- The maternal and fetal NOAEL is 1.2 mg/kg/day.

Methods

Doses:	0, 0.12, 0.4, and 1.2 mg/kg/day (0, 0.06, 0.2, and 0.6 mg/mL oligonucleotide content, respectively)
Frequency of dosing:	Once daily
Dose volume:	2 mL/kg
Route of administration:	IV bolus injection

Formulation/Vehicle:	Phosphate buffered saline (PBS)
Species/Strain:	New Zealand White rabbits
Number/Sex/Group:	20
Satellite groups:	
Study design:	The rabbits were dosed from GD7 through 19 and were sacrificed on GD29.
Deviation from study protocol:	None with an impact in the integrity of the study

Observations and Results

Mortality (Daily)

None

Clinical Signs

One mid-dose female (No. 3518) aborted on GD 25. This female was considered normal for clinical observations until GD 25 where red vaginal discharge and ungroomed fur was documented. The doe did not show body weight loss and had no gross pathology findings. At the time of discovery, the litter size was 10 pups total, 9 live and 1 dead. The uterine exam revealed 10 implantation sites with 0 early or late resorptions. In the Study Report, this abortion was considered spontaneous and not test article-related because it was a single non-dose dependent event. This reviewer agrees; the rabbit is known to be prone to spontaneous abortion.

Body Weight (Daily)

No test article-related effects in body weight, body weight gains, or gravid uterus adjusted body weights

Feed Consumption (Daily)

No test article-related effects

Toxicokinetics (GDs 6 and 19 at 0, 5 min, and 1, 3, 8, and 24 hours postdose)

Exposure generally increased in a more than dose proportional manner over the dose range tested on both GD 7 and GD 19 (Table 15). There was no accumulation following repeated IV bolus administrations. On GD 7 and GD 19, ARC1905 (Zimura) concentrations generally stayed above LLOQ up to the last timepoint for the 0.4 and 1.2 mg/kg/day dose groups and up to the 8 hr timepoint for the 0.12 mg/kg/dose group

Table 16: Summary of TK Parameters – Embryofetal Developmental Toxicity Study in Rabbits

		Treatment		
		0.12 mg/kg Zimura	0.4 mg/kg Zimura	1.2 mg/kg Zimura
Day	TK Parameter	Mean		
GD 7	C_0 (ng/mL)	3620	8870	41700
	AUC_{tlast} (h*ng/mL)	4260	19200	78800
	AUC_{0-24} (h*ng/mL)	4470	20400	82200
	AUC_{inf} (h*ng/mL)	4310	19600	80100
	$t_{1/2}$ (h)	1.25	2.13	2.35
	CL (mL/h/kg)	27.9	20.5	15.0
	Vss (mL/kg)	31.4	44.5	36.3
GD 19	C_0 (ng/mL)	2770	7470	35700
	AUC_{tlast} (h*ng/mL)	4240	18200	81300
	AUC_{0-24} (h*ng/mL)	4550	18600	81300
	AUC_{inf} (h*ng/mL)	4320	18300	81600
	$t_{1/2}$ (h)	1.43	2.27	3.15
	CL (mL/h/kg)	26.7	21.6	14.9
	Vss (mL/kg)	15.5	43.7	43.6
	RA C_0	0.773	0.844	0.857
	RA AUC_{tlast}	0.999	0.955	1.03
	RA AUC_{0-24}	1.02	0.914	0.986

RA = Ratio of Accumulation

Source: Table 3.2.1, Appendix 16 TK Evaluation Report

Mean CL values were less than liver blood flow in a 2.5-kg rabbit (4248 mL/hr/kg), indicating that avacincaptad pegol is not highly extracted by the liver. Mean Vss values did not exceed the total body water of a 2.5-kg rabbit (716 mL/kg) and was similar to plasma volume (44 mL/kg), indicating that avacincaptad pegol did not highly distributed to the tissues, and was largely restricted to the vascular space.

Dosing Solution Analysis

The concentrations of dose formulations collected on the first and last day of preparation were within 100 to 104% of the nominal value.

Necropsy (GD 29)

No test article related effects were observed in organ examined (cervix, ovary, uterus).

Note: There is a mistake in Study Report Table 6 "Summary of Macroscopic Findings" as it shows that no high-dose animal was examined. Individual animal listings confirm the animals in this dose group were examined.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

No test article-related effects

Offspring (Malformations, Variations, etc.)

Umbilicus hernia, gastroschisis, or distended abdomen were observed each in one fetus of a separate litter as listed below.

- Low dose Fetus No. 2515-1 - Umbilicus, hernia – malformation (Intestines protrude); Intestine, malpositioned – malformation (intestines protrude through umbilicus)
- Low dose Fetus No. 2519-7 - Trunk, gastroschisis (liver and small intestine) (malformation); Intestine, malpositioned - malformation, small intestine protrudes through abdominal opening
- High dose Fetus No. 4508-9 – distended abdomen (variation)

These are rare abnormalities (low background incidence) but do not appear related to the test article because the observations were not dose dependent and/or the observations were limited to one fetus from one litter in the dose group. In addition, the litter/fetal incidence was similar to performing lab historical control data (2016 through 2020) submitted by the Applicant (Appendix 14).

Other findings with higher incidence in the high dose included sternebra (fused), and thoracolumbar supernumerary rib (Table 16, excerpts from Study Report incidence table). The litter/fetal incidence for the sternebra variation was similar to performing lab historical control data submitted by the Applicant (Appendix 14), but it was slightly higher in the high dose for supernumerary rib (thoracolumbar).

Table 17: Fetal findings with Increased Incidence – Rabbit Embryofetal Developmental Toxicity Study

Exam Type: Skeletal		0 mg/kg/day Group 1	0.12 mg/kg/day Group 2	0.4 mg/kg/day Group 3	1.2 mg/kg/day Group 4
Number of Fetuses Examined:		158	181	153	197
Number of Fetuses Evaluated:		158	181	154	197
Number of Litters Examined:		15	18	16	20
Number of Litters Evaluated:		15	18	16	20
Sternebra					
Sternebra, 1 or more, Fused - Variation	Fetuses N(%)	1(0.39)	3(1.39)	1(0.63)	6(2.71)
	Litters N(%)	1(6.7)	2(11.1)	1(6.3)	5(25.0)
Supernumerary rib					
Thoracolumbar, 1 or more, Full - Variation	Fetuses N(%)	38(20.60)	34(20.66)	33(24.11)	56(28.92)
	Litters N(%)	11(73.3)	14(77.8)	10(62.5)	18(90.0)

Historical control data (2016 through 2020):

- Sternebra, fused – Litter incidence: 0-35.5%; Fetal incidence: 0-5.4%
- Supernumerary rib – thoracolumbar, full - Litter incidence: 0-75%; Fetal incidence: 0-27.9%

In the rat, there was an increase incidence of short thoracolumbar supernumerary rib (see below). Therefore, the higher incidence of full thoracolumbar

supernumerary rib in rabbits at the high dose appears to be test article related, but it is not considered adverse.

Study title: An Embryo-Fetal Development Study of Zimura Given by Intravenous Injection in Rats

Study no.:	20334075
Study report location:	DocuBridge Module 4.2.3.5.2 \\CDSESUB1\EVSPROD\nda217225\0004\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42352-embryo-fetal-dev\20334075\20334075.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 27, 2022
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ARC1905, Zimura™ (Avacincaptad Pegol Sodium) Injection (oligonucleotide content: 19.9 mg/mL), batch/lot no. 3-FIN-4019, ≥85.0% pure AX-HPLC), ≥90.0% pure (IP-HPLC)

Key Study Findings

- There were no adverse findings on any maternal or fetal parameter.
- Compared to controls, there was a dose-dependent increased incidence of short thoracolumbar supernumerary ribs (also defined as an ossification site without distal cartilage) in all ARC1905-treated groups.
- As determined by the Applicant, this finding is considered a non-adverse variation as these areas of ossification that are without distal cartilage are most probably and frequently absorbed into the lateral processes of the adjacent vertebrae. As such, they may simply be a minor variant in the normal developmental process and may resolve into the vertebral arch later in development.
- The maternal and fetal NOAEL was considered to be 1.2 mg/kg/day.

Methods

Doses:	0, 0.1, 0.4, and 1.2 mg/kg/day (0, 0.05, 0.2, and 0.6 mg/mL oligonucleotide content, respectively)
Frequency of dosing:	Once daily
Dose volume:	2 mL/kg
Route of administration:	IV bolus injection
Formulation/Vehicle:	PBS
Species/Strain:	Crl:CD(SD) Sprague-Dawley rats

Number/Sex/Group: 24
Satellite groups: TK evaluation: 6 rats per test article-treated groups; 3 rats in control group
Study design: The rats were dosed from GD 6 through GD 17. The animals in the main study were sacrificed on GD 21 and those in the TK phase on GD 18.
Deviation from study protocol: None with an impact in the integrity of the study

Observations and Results

Mortality (2X/day)

None

Clinical Signs (Daily)

No test article-related effects

Body Weight (Daily)

No test article-related effects in body weight, body weight gains, or gravid uterus adjusted body weights

Feed Consumption (Daily)

No test article-related effects

Toxicokinetics (GDs 6 and 17 at 0, 5 min, and 1, 3, 8, and 24 hours postdose)

ARC1905 plasma exposures increased with dose but generally in a less than dose proportional manner. There was no accumulation with repeat dosing from GD6 to Day 17.

The TK parameters are summarized in Table 17.

Table 18: Toxicokinetic Parameters – Rat Embryofetal Developmental Toxicity Study

Day	Treatment	C_0 (ng/mL)	AUC_{last} (h*ng/mL)	$AUC_{0\text{-}24}$ (h*ng/mL)	AUC_{inf} (h*ng/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	Vss (mL/kg)	RA C_0	RA AUC_{last}	RA $AUC_{0\text{-}24}$
GD 6	0.1 mg/kg Zimura	2640	12600	12600	12900	4.80	7.72	43.0	NA	NA	NA
	0.4 mg/kg Zimura	8420	45600	45600	48500	5.91	8.25	58.6	NA	NA	NA
	1.2 mg/kg Zimura	26500	128000	128000	138000	6.23	8.71	65.3	NA	NA	NA
GD 17	0.1 mg/kg Zimura	2030	9440	9440	10400	6.87	10.6	95.8	0.769	0.751	0.751
	0.4 mg/kg Zimura	7400	50000	50000	55200	7.30	8.00	71.6	0.879	1.10	1.10
	1.2 mg/kg Zimura	25700	131000	131000	143000	6.63	9.14	79.7	0.969	1.03	1.03

RA = Ratio of Accumulation
NA = Not Applicable

For reference, clinical exposure is 68.4 ng/mL
Source: Table 3.2.1, Appendix 17 TK Report

Clearance values were less than liver blood flow in a 0.25 kg rat (3312 mL/hr/kg), indicating that avacincaptad pegol was not highly extracted by the liver. Vss values did not exceed the total body water of a 0.25 kg rat (668 mL/kg) and was ≤3X higher than plasma volume (31.2 mL/kg), indicating that avacincaptad pegol was not highly distributed to the tissues, and was largely restricted to the vascular space.

Dosing Solution Analysis

The concentrations of dose formulations collected on the first day of preparation were within 100 to 104% of the nominal value. The results from the last preparation for Group 2 (0.314 mg/mL; 628%) and Group 4 (0.0462 mg/mL; 7.7% were out of specification. This was likely the result of samples being transferred into incorrect sample vials. i.e., Group 2 (0.05 mg/mL) formulation was sampled and transferred into the Group 4 (0.6 mg/mL) sample containers and the Group 4 (0.6 mg/mL) formulation was sampled and transferred into the Group 2 (0.05 mg/mL) sample containers. With the supposition that the two sample groups were switched, then the measured values for the 0.05 mg/mL formulation (0.0508 mg/mL/102%) and 0.6 mg/mL formulation (0.609 mg/m /101%) were within specification. The TK analysis support this was the case as there was a dose related increase in plasma exposure.

Necropsy (GD 21)

No test article-related findings

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

No test article-related findings

Offspring (Malformations, Variations, etc.

The following variation was observed which occurred in a dose-dependent manner: 1 or more short thoracolumbar supernumerary ribs (also defined as an ossification site without distal cartilage) in 6 (4 litters), 11 (6 litters), 11 (6 litters), and 25 (10 litters) fetuses in the 0, 0.1, 0.4, and 1.2 mg/kg/day dose group, respectively (Table 18, excerpts from the Study Report).

Table 19: Increased Incidence of Short Thoracolumbar Supernumerary Rib – Rat Embryofetal Developmental Toxicity Study

Exam Type: Skeletal		0 mg/kg/day Group 1	0.1 mg/kg/day Group 2	0.4 mg/kg/day Group 3	1.2 mg/kg/day Group 4
Number of Fetuses Examined:		138	150	149	145
Number of Fetuses Evaluated:		265	286	284	281
Number of Litters Examined:		23	24	24	24
Number of Litters Evaluated:		23	24	24	24
Sternebra					
Sternebra, 1 or more, Misshapen - Variation	Fetuses N(%)	0(0.00)	0(0.00)	1(1.04)	1(0.69)
	Litters N(%)	0(0.0)	0(0.0)	1(4.2)	1(4.2)
Sternebra, 1 or more, Sternoschisis - Malformation	Fetuses N(%)	0(0.00)	0(0.00)	1(0.52)	0(0.00)
	Litters N(%)	0(0.0)	0(0.0)	1(4.2)	0(0.0)
Sternebra, 1 or more, Unossified - Variation	Fetuses N(%)	0(0.00)	2(1.19)	1(1.04)	0(0.00)
	Litters N(%)	0(0.0)	2(8.3)	1(4.2)	0(0.0)
Supernumerary rib					
Cervical, 1 or more, Short - Variation	Fetuses N(%)	2(1.45)	1(0.60)	3(2.60)	2(1.53)
	Litters N(%)	2(8.7)	1(4.2)	3(12.5)	2(8.3)
Thoracolumbar, 1 or more, Short - Variation	Fetuses N(%)	6(4.24)	11(6.94)	11(7.04)	25(16.23)
	Litters N(%)	4(17.4)	6(25.0)	6(25.0)	10(41.7)

Source: Study Report, Table 9

The Applicant did not provide historical control data for this finding. Values from historical control data from WIL labs (1998-2010)[3]:

Litter %: Mean 7.0 ± 3.15; Range: 0 to 18.9%

As noted under the waiver justification (see Section 9.1 Fertility and Embryonic Development of this review), a similar finding was observed with avacopan (a small molecule complement 5a receptor antagonist) in hamsters. The finding was not considered adverse for avacopan, but it was acknowledged in the label. Similarly, the Applicant concluded for avacincaptad pegol (see page 8, Module 1.12.13):

- This abnormality was considered a non-adverse variation (i.e., would not be expected to affect long-term survival) since no other skeletal observation was attributed to maternal exposure to avacincaptad pegol and fetal growth was not impacted.
- This finding is also considered a non-adverse variation as these areas of ossification that are without distal cartilage are most probably and frequently absorbed into the lateral processes of the adjacent vertebrae. As such, they, may simply be a minor variant in the normal developmental process and may resolve into the vertebral arch later in development.

One fetus at the high dose showed edema of the entire subcutis. However, the fetal (0.30%) and litter incidence (4.2%) was within historical control data from the

[3] Mylchreest E. and Harris S. B., Historical Control Data in Reproductive and Developmental Toxicity Studies: Data Interpretation: Using Historical Control Data to Understand Supernumerary Ribs, a Common Skeletal Variation, Teratogenicity Testing: Methods and Protocols, Barrow PC. Humana Press, 2013, pages 290 - 292.

performing lab (0-0.5% and 0-4.8%, respectively, Study Report Appendix 14). Therefore, the finding was not considered test article related.

9.3 Prenatal and Postnatal Development

No studies were conducted. See Section 9.1 of this review for Applicant request for waiver to conduct these studies.

11 Integrated Summary and Safety Evaluation

Pharmacology

The studies presented showed that avacincaptad pegol binds to human C5 with high affinity and specificity and is an inhibitor of C5 cleavage (as measured by decreased formation of C5a) and inhibits complement activity after activation of the classical and/or alternative complement pathways.

Avacincaptad pegol did not activate complement in vitro (as assessed by C3a and/or Bb generation in human serum in vitro at concentrations ≥ 2 mg/mL) or in vivo in cynomolgus monkeys administered IV doses of up to 1410 mg/kg daily for up to 7 days.

In vivo results with cynomolgus monkeys confirmed that plasma avacincaptad pegol concentrations > 130 µg/mL provided complete inhibition of complement activity after ex vivo activation of the classical and alternative complement pathways. Lower concentrations resulted in less than complete inhibition. The in vivo studies, however, did not determine a dose with no activity.

Based on in vitro data demonstrating $1/10^{th}$ of the potency of avacincaptad pegol for cynomolgus monkey C5, the target concentration for avacincaptad pegol in cynomolgus monkey plasma after IV dosing was projected to be 10 µM (130 µg/mL). Based on this fact, it seems we can assume plasma concentrations of approximately 10 µg/mL will be required in humans for complete C5 inhibition. The clinical C_{max} was 68.3 ng/mL, over 140X lower than the estimated concentration for complete C5 inhibition.

Avacincaptad pegol was not associated with QT prolongation or significant safety pharmacology effects (CNS, cardiovascular, and respiratory).

Avacincaptad pegol showed weak affinity for protamine in vitro (based on data from an identical aptamer, ARC187). A pharmacodynamic drug interaction study showed that avacincaptad pegol (ARC187 mean plasma concentration up to 13.60 µM (175 µg/mL) did not interfere with heparin or protamine activity in vivo in rats.

Effects considered unrelated to C5 inhibition were limited to anticoagulation (prolongation of APTT). Avacincaptad pegol showed mild anticoagulant properties at

high concentrations (2 mg/mL) in human plasma in vitro. Similar results were observed for ARC594 (a non-C5 specific aptamer of similar size and PEG content), suggesting that the observed effects on coagulation may be characteristic of aptamers in general. Transient prolongation of APTT and PT has also been observed with other antisense oligonucleotides and seems to be a class effect.

Increased APTT prolongation was observed at high plasma concentrations in IV toxicity studies in rats and monkeys. In the 7-day IV toxicity studies, A NOEL was not identified. Overall, exposure margins were > 500X the clinical plasma exposure (C_{max} and AUC). In the monkey cardiovascular safety pharmacology study, the C_{max} at the NOEL of 10 mg/kg for the increased in APTT values is 3216X higher than the mean plasma exposure observed at the recommended clinical dose (≤68.4 ng/mL).

A marginal increase in APTT was noted in the dog 9-month IVT toxicity study at the high dose (3 mg/eye). The finding was not observed during recovery. The finding was considered potentially test article related. As noted below, an internal recommendation was given for monitoring APTT and PT in the clinic after review of the initial IND (see further details below).

Ocular Toxicity Studies

Repeat-dose IVT toxicity studies were conducted in New Zealand White rabbits (0, 0.15, 0.5, and 1.5 mg/eye) and Beagle dogs (0, 0.3, 1, and 3.0 mg/eye). The studies included a combination arm of the high dose plus Lucentis®. The main finding in both species was vacuolation of the ganglion cell layer of the retina observed upon microscopic evaluations. In the dog, vacuolation of the optic tract in the brain was also observed. Coadministration with Lucentis® did not impact these findings.

In the rabbit, the finding was focal and only present at the high dose (ARC1905 1.5 mg/eye ± Lucentis 0.3 mg/eye) as early as Day 4 after a single IVT injection. The severity was minimal to moderate. The finding was reversible following a 1-month recovery period (Day 29). On Week 37 (after 10 monthly doses), mild retinal vacuolation was observed in the high dose group. The finding did not increase in severity between Doses 1 and 10. The finding was again reversible following a 4-week recovery period (Day 281). The NOEL in the rabbit was the mid dose, 0.5 mg/eye.

In the dog, the retinal vacuolation was present at all dose levels (0.3, 1.0, and 3.0 mg/eye ± Lucentis 0.5 mg/eye), although initially (Day 4), it was only present at ≥1.0 mg/eye (minimal to moderate and focal). These findings were reversed following a one-month recovery period. After 10 monthly doses (Week 37), minimal to moderate focal retinal vacuolation was observed at all test article doses (± Lucentis®). Mild to moderate diffuse retinal vacuolation was observed at the high dose (3.0 mg/eye ARC1905 ± 0.5 mg/eye Lucentis®). In addition, secondary vacuolation (mild) of the optic tract in the brain was also observed at 3.0 mg/eye. The retinal vacuolation was reversible in the optic tract and still present (minimal to mild) in the retinal ganglion cell layer after a 4-week recovery period. Therefore, at Week 37, a NOEL for avacincaptad pegol-related

retinal vacuolation was not identified. The findings at 0.3 and 1.0 mg/eye avacincaptad pegol were limited to minimal to mild focal retinal vacuolation.

The presence of the vacuoles most likely reflects uptake of the PEGylated aptamer within the retinal cells (i.e., the vacuoles may occur due to the presence of the PEG polymer conjugated to the aptamer). These findings were considered non-adverse as there were no adverse test article-related effects on ocular histopathology and no noticeable ERG changes. These findings were mostly reversible in both species. The observed retinal vacuolation at the highest tested dose of 3.0 mg/eye in beagle dogs would likely resolve given additional recovery time as it showed decreased severity.

In rabbits receiving the combination of 1.5 mg/eye ARC1905 + 0.3 mg/eye Lucentis®, inflammation within the vitreous humor and, in some cases, panuveitis was noted with higher frequency starting at Week 5 (after the 2nd IVT dose) and increasing in severity with continued dosing. The inflammation was associated with alterations in ERG parameters and changes in IOP. Other findings observed in animals receiving 1.5 mg/eye ARC1905 + 0.3 mg/eye Lucentis® included increased incidence of corneal opacities, vacuolar degeneration of the optic tract in the brain, marked diffuse retinal atrophy, fibrinous accumulation in the anterior and posterior chambers, cataract, chronic inflammation of the choroid, and marked posterior chamber abscess formation. These findings were limited to the animals with severe inflammation and could be related to an immune reaction to Lucentis® (a human protein, which is likely to be immunogenic in rabbits). However, the lack of evaluation of a Lucentis® alone group precludes a definitive assessment of a potential interaction between both molecules in the development of the inflammatory response.

Ocular NOAEL Determination

Rabbit: Based on the retinal vacuolation, the NOEL for avacincaptad pegol is 0.5 mg/eye for single and repeated IVT injections. The vacuolation was mostly of mild severity, reversible, and not associated with histopathological adverse changes (i.e., retinal degeneration, inflammation, necrosis) and noticeable effects on ERG measurements, therefore, it appears not to be adverse. In the absence of observed adverse effects at the doses examined, the NOAEL for avacincaptad pegol is considered to be ≥ 1.5 mg/eye.

Dog: Based on the retinal vacuolation, there was no NOEL following a single or repeated IVT injections. Given the more diffuse retinal vacuolation observed at 3.0 mg and extension of the finding to the optic tract, a conservative approach was used to select the NOAEL. The NOAEL is considered to be 1.0 mg/eye even though optic tract vacuolation at 3.0 mg/eye was not associated with any adverse histopathology or significant ERG findings.

The IVT exposure margins at the NOEL and NOAEL in rabbits and dogs are shown in the table below. This reviewer did not account for differences in pharmacological activity per species as 1) it was not done throughout development, and

2) key findings for the proposed indication and dosing regimen are more likely due to the PEG (tissue vacuolation) or characteristics of aptamers (APTT/PT changes), and unrelated to C5 inhibition. Additional information about species selection and why exposure margins are not corrected for differences in pharmacological activity is found under Section 4.4 of this review.

Table 20: Ocular Exposure Margins

Toxicity	Species	NOEL/NOAEL (mg/eye)	NOEL/NOAEL (mg/mL vitreous)	Safety Margin Based on mg/mL vitreous* at MRHD or 2 mg/eye (0.5 mg/mL vitreous)
Retinal vacuolation (minimal to moderate)	Rabbits	NOEL: 0.5	0.33	0.66X
		NOAEL: 1.5	1	2X
Retinal vacuolation (minimal to moderate)	Dogs	NOEL: not identified	---	---
		NOAEL: 1.0	0.33	0.66X
Optic tract vacuolation (mild)	Dogs	NOEL: 1.0 NOAEL: 1.0	0.33	0.66X

*Calculations based on vitreous volumes of 1.5 mL (rabbit), 3.0 mL (dogs), and 4 mL (humans)
MRHD: Maximal recommended human dose

The Applicant explained that greater doses could not be used via the IVT route of administration, as the maximum feasible dose in these studies was determined based on the aptamer solution viscosity (solutions above 30 mg/mL oligonucleotide concentration are too viscous) and injection volume (maximum of 50 µL and 100 µL/injection for rabbit and dog eyes, respectively).

The Applicant indicated that a favorable safety profile has been shown at a monthly clinical dose of 4 mg avacincaptad pegol over an 18-month period (Study OPH2003, Module M.5.3.5.1). Therefore, the clinical data support little or no risk to either the integrity of the eye or vision is expected from a clinical dose at the lower established MRHD (i.e., 2 mg once monthly IVT injection). In communications with the clinical review team, vacuolation was not observed in the clinical trials as assessed by optical coherence tomography (OCT).

Systemic Findings Following IVT Administration

After IVT administration in NZW rabbits and beagle dogs, there were no adverse systemic effects up to the highest dose evaluated. In the dog, there were marginally increased APTT values at the high IVT dose (ARC1905 3 mg/eye ± Lucentis® 0.5 mg/eye) from Week 13 onward. The finding was not present following a 4-week

recovery period. At the highest dose, the plasma C_{max} value after 10 monthly IVT doses was 43.3 ng/mL in rabbits and 488.7 ng/mL ng/mL in dogs, which is 0.63-fold and 7-fold the human C_{max} (68.4 ng/mL) value at the recommended human dose of 2 mg, respectively. After review of the initial IND, an internal recommendation was given for monitoring APTT and PT in the clinical trials. Per the Applicant, effects on coagulation (APTT and PT) were monitored in the clinic (Study OPH2000; doses of 0.3, 1, and 2 mg for at least 6 months) with no adverse effects observed.

Systemic Toxicity Studies

IV toxicity studies of up to 7-days duration were conducted in Sprague-Dawley rats and cynomolgus monkeys. In the rat 7-day IV toxicity study (0, 367, 760 or 1410 mg/kg/day), primary findings included hematology (decreases in RBC, WBC, platelets), increased APTT and PT values, clinical chemistry (increase glucose and urea levels, decrease in cholesterol, triglyceride, total protein and albumin), organ weights (increased liver, popliteal lymph node, adrenal, and spleen weights and decreased thymus weight), and histopathology (vacuolation, basophilia and/or hypertrophy/hyperplasia and/or infiltration of macrophages in multiple tissues) at all doses evaluated (≥ 367 mg/kg). In the thymus and bone marrow, lymphoid atrophy/necrosis and myeloid/erythroid hypocellularity, respectively, were noted at ≥760 mg/kg. Except for the thymus and bone marrow, the presence of ARC1905 related vacuoles in tissue macrophages was not associated with evidence of degeneration or inflammation in tissue and parenchymal cells of organs. Reversibility or partial reversibility was noted in most findings except for macrophage hypertrophy/hyperplasia with vacuolation in histological examination following a 14-day recovery period.

In the monkey 7-day IV toxicity study (0, 0, 141, 423, or 1410 mg/kg/day), mortalities occurred at 1410 mg/kg/day and were attributed to cardiopulmonary failure resulting from hemorrhage and edema in the heart (myocardium) and lungs. Other adverse effects included anticoagulation, increased incidence of rouleaux formation, anemia, thrombocytopenia, and hypoproteinemia. APTT was prolonged at ≥423 mg/kg and PT at 1410 mg/kg. Organ weight changes included increased liver, popliteal lymph node, adrenal, kidney, lung, and heart weights. Microscopic findings included basophilic granules, basophilic swirled material, and basophilic vacuolization of macrophages in almost every tissue. Most clinical pathology findings were reversible or partially reversible. Vacuolation in macrophages was still present in multiple tissues at the end of the recovery period (Day 22).

A NOAEL was not identified in the 7-day IV toxicity studies. At the low dose in each study (367 mg/kg/day in rats and 141 mg/kg/day in monkeys), exposure margins are over 1000X (rat) and 540X (monkey) the systemic exposure observed in humans at recommended dose of 2 mg (AUC_{0-t} of 999.9 ng•day/mL or 23.99 µg•hr/mL). Therefore, it is considered unlikely that systemic tissue vacuolization and other adverse effects identified in the 7-day continuous IV dose studies will occur at the systemic exposures expected to be observed in humans at the intended dosing regimen.

The exposure margins for the systemic toxicity studies are shown in the Table 14, under Section 8. Carcinogenicity of this review.

Embryofetal Developmental Toxicity (EFD) Studies

In the EFD study in rats, no teratogenic effects were observed up to 1.2 mg/kg/day. A dose-dependent increase (≤2.4X compared to concurrent and historical control range) in the incidence of a skeletal variation (short thoracolumbar supernumerary rib) was observed at all avacincaptad pegol dose levels. This abnormality was considered a non-adverse variation (would not be expected to affect long-term survival) since no other skeletal observation was attributed to maternal exposure to avacincaptad pegol and the lack of any other signs of developmental toxicity. Additionally, this finding is considered a developmental delay and can resolve into the vertebral arch later in development. At 1.2 mg/kg/day in rats, systemic exposure to avacincaptad pegol is 5.5 times higher than the MRHD, based on AUC. A similar finding was observed in hamsters for avacopan (see TAVNEOS Prescribing Information, 2021), a complement 5a receptor antagonist for oral use. The data from both products with similar pharmacology support that the finding, although not adverse, appears to be a class effect.

In the EFD study in rabbits, there was no avacincaptad pegol-related adverse effect on any measured maternal or fetal parameter up to 1.2 mg/kg/day (NOAEL). Compared to controls, there was an increased incidence of full thoracolumbar supernumerary ribs at the high dose. The increase was slightly above (1.2X) the concurrent control and historical control range. Considering the high spontaneous variability of this finding in rabbits, marginal increase, and the lack of any other signs of developmental toxicity, the finding is also considered a non-adverse variation. Systemic exposure to avacincaptad pegol at the NOAEL, is 3.4 times higher than the MRHD.

The exposure margins for the findings of supernumerary ribs are shown below (Table 20). Note that the exposure margins are different to those reported by the Applicant on Table 14. It is unclear to this reviewer how the applicant exposure margins were calculated.

Table 21: Ocular Exposure Margins for Supernumerary Ribs – EFD Studies

Species	Finding	NOAEL		Safety Margin Based on AUC*
		mg/kg/day	AUC (ng•hr/mL) C_{max} (ng/mL)	
Rat	Increased incidence of short thoracolumbar supernumerary ribs	1.2	AUC: 131000 C_{max}: 25700	AUC: 5.5X C_{max}: 376X
Rabbits	Increased incidence of full thoracolumbar supernumerary ribs	1.2	AUC: 81300 C_{max}: 35700	AUC: 3.4X C_{max}: 522X

AUC_{last} and C_{max} values are from GD 17 (rats) GD 19 (rabbits)
Human C_{max} = 68.4 ng/mL and AUC_{0-t} value at 2 mg once monthly was 999.9 ng•day/mL (23.998 µg•hr/mL)

It is scientific knowledge that supernumerary rib is one of the most common skeletal variants in rodent and rabbit developmental toxicity studies. Supernumerary rib, unilaterally or bilaterally, located at the thoracolumbar border is a common variant in these species with short supernumerary rib much more common than full supernumerary rib in the rat, whereas both short and full supernumerary rib are much more common in the rabbit. Based on the prevalence of supernumerary rib in the population, marginal increases in the incidence of this finding in treated groups may not have toxicological or biological significance. Per recommendations in Mylchreest E. and Harris SB[3], because of the high variability and spontaneous incidence, short (rudimentary) ribs in rats and supernumerary rib (rudimentary or full) in rabbits should not be considered biologically significant in the absence of more profound signs of developmental toxicity, i.e., increased incidences of malformations, embryolethality, or fetal weight reduction.

Based on the increased incidence of thoracolumbar supernumerary ribs in rats and rabbits for avacincaptad pegol and in the hamster for another C5 inhibitor (avacopan), the finding appears to be a class effect, as noted above. However, given the explanation given above, the finding does not appear to be clinically relevant. See separate review for labeling recommendations for this NDA.

Genetic Toxicity Studies

Avacincaptad pegol was negative in the bacterial reverse mutation assay, chromosomal aberration in mammalian cells and in vivo mouse bone marrow micronucleus assays.

Carcinogenicity and Fertility/Early Embryonic Development and Pre-/Postnatal Development Studies

The Applicant submitted a justification not to conduct the studies. See Section 8. Carcinogenicity and 9. Reproductive and Developmental Toxicology of this review. The Pharmacology/Toxicology team concluded that the weight of evidence supports that the studies are not necessary for the intended dosing regimen and indication.

Conclusion and Recommendations:

In conclusion, the nonclinical data support that ocular retinal vacuolation could occur at the intended clinical dose. The finding was not associated with any evidence of disrupted retinal structure or function as assessed by histopathology or noticeable ERG changes, and therefore, appears non-adverse. The nonclinical finding was addressed with the clinical team throughout drug development and careful monitoring for retinal abnormalities was recommended. At the end-of-Phase 2 stage, the nonclinical team reported that exposure margins in the chronic ocular toxicity studies were low, however existing clinical data were used to mitigate nonclinical concern. A similar finding was not observed in the clinical studies on assessment by OCT.

Pharmacology/Toxicology team supports approval of avacincaptad pegol for treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

For final nonclinical labeling recommendations, see separate label review for this NDA.

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/s/

MARIA I RIVERA
05/26/2023 11:11:58 AM

KIMBERLY P HATFIELD
05/30/2023 01:21:07 PM
I concur with the review and recommendations of Dr. Rivera. Acting and signing on behalf of Dr. Lori Kotch.