CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217225Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	217225
Link to EDR	\\CDSESUB1\evsprod\NDA217225\0001
Applicant	Iveric Bio
Proposed Brand Name, Drug, Dosage Form and Strength	Izervay
Submission Type	Priority
Submission Date	12/19/2022
PUDFA Goal Date	8/19/2023
Proposed Indication	For treatment of Geographic Atrophy (GA) secondary to age-related macular degeneration (AMD)
Proposed Dosing Regimen & Instructions	2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection once monthly (approximately 28 ± 7 days)
Associated IND	77902
OCP Division	DIIP
OCP Review Team	Amit A. Somani, B. Pharm., Ph. D. Senior Clinical Pharmacology Reviewer and Pharmacometrics Reviewer Youwei Bi, Ph.D. Pharmacometrics Team Leader, DPM Ping Ji, Ph. D. Clinical Pharmacology Team Leader, DIIP
OCP Final Signatory	Ping Ji., Ph. D.

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1. EXECUTIVE SUMMARY

This submission is a 505(b)(1) NDA for IZERVAY [avacincaptad pegol (also known as ARC1905 or Zimura)], which is a 2 mg (0.1 mL of 20 mg/mL solution) for ophthalmic intravitreal (IVT) injection for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

Pharmacokinetic (PK) data for proposed to-be-marketed (TBM) avacincaptad pegol was collected in phase 1 study OPH2000. The clinical pharmacology review was focused on reviewing PK and Population (Pop) PK information for avacincaptad pegol from Study OPH2000.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the relevant Clinical Pharmacology information provided by the Applicant in NDA 217225 for avacincaptad pegol solution for IVT injection and recommends approval of this NDA. The key review issues with specific clinical pharmacology recommendations and comments are summarized in **Table 1**.

Table 1. Clinical Pharmacology Recommendations and Comments

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Pivotal evidence of effectiveness is derived from two Phase 3 studies: Studies OPH2003 and ISEE2008. See clinical review for additional details.
General dosing instructions	2 mg (0.1 mL of 20 mg/mL solution) administered by IVT injection once monthly (approximately 28 ± 7 days). The proposed dosing regimen was evaluated in two pivotal phase 3 studies (OPH2003 and ISEE2008).
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustments based on any intrinsic or extrinsic factors are recommended.
Labeling	Labeling recommendations are not finalized at the time of this review and discussions on labeling language are ongoing.
Bridge between the to-be-marketed (TBM) and clinical trial formulations	A bridging pharmacokinetic (PK) study between the TBM and clinical trial formulation is not warranted since no change in formulation was made throughout the development program as per the Applicant

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

Avacincaptad pegol is an RNA aptamer, a PEGylated oligonucleotide that binds to and inhibits complement protein C5. By inhibiting C5, avacincaptad pegol prevents its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b [the initiating subunit of the membrane attack complex (MAC or C5b-9)] thus preventing MAC formation.

Pharmacokinetics

The Study OPH2000 evaluated the safety, tolerability, and PK profile of avacincaptad pegol IVT injection when administered in combination with multiple doses of Lucentis 0.5 mg in patients with nAMD. See Appendix 4.3 of this review for details.

Absorption/Distribution: Maximum avacincaptad pegol plasma concentrations (C_{max}) are estimated to occur approximately 7 days post-dose. Mean free avacincaptad pegol plasma C_{max} is estimated to be 68.4 ng/mL (57.8%) in neovascular AMD (nAMD) patients. Although not directly measured in the vitreous, no or minimal accumulation of avacincaptad pegol is expected in the vitreous or plasma following monthly repeat administration. In humans, plasma avacincaptad pegol concentrations are predicted to be approximately 7,000-fold lower than vitreal concentrations. The maximum concentration of avacincaptad pegol in the vitreous humor is expected to be 500 µg/mL (500,000 ng/mL) immediately after the first injection assuming an homogeneous distribution in a vitreous volume of 4 mL (i.e., 2000 µg / 4 mL). Given a C_{max} of 69.9 ng/mL after the first injection based on PopPK analysis, the systemic exposure to avacincaptad pegol after the first dose is 7,000 times lower than that expected in the vitreous humor.

Based on a PopPK analysis of patients with nAMD, maximum plasma concentrations are predicted to be reached at approximately 90 days after monthly IVT administration of avacincaptad pegol 2 mg. See Section 4.2 for details of the PopPK analysis.

Metabolism/Elimination: Avacincaptad pegol is a RNA aptamer. Avacincaptad pegol is expected to be catabolized by endonucleases and exonucleases to oligonucleotides of shorter lengths which may be excreted renally, in similar manner to the elimination of endogenous RNA. The metabolism of avacincaptad pegol has not been fully characterized. The estimated

half-life of avacincaptad pegol is approximately 12 days.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing regimen is 2 mg (0.1 mL of 20 mg/mL solution) administered by IVT injection once monthly (approximately 28 ± 7 days).

2.2.2 Therapeutic individualization

The therapeutic individualization is not needed.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

Labeling recommendations are not finalized at the time of this review and discussions on labeling language are ongoing.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Avacincaptad pegol is a PEG-conjugated RNA aptamer. RNA-based aptamers, like avacincaptad pegol, are chemically synthesized small molecules not derived from biological systems. Avacincaptad pegol is an inhibitor of complement activation that acts by binding to human C5 with high affinity (KD = 0.69 ± 0.148 nM at 37°C) and specificity.

Some of the key regulatory interactions during the development of avacincaptad pegol are stated below:

- Type B, Pre-IND Meeting - May 5, 2005
- Fast Track Designation - Apr 1, 2020 (Fast Track Designation Grant Letter)
- Type C, Clinical Pharmacology Meeting - Dec 6, 2021
  - Dissussed the PK assessment plan in a PK sub-study within ISEE2008, bioanalytical methodology, and PopPK model aspects
  - *Reviewer comment: Even though the Applicant had initially planned to*

have the PK data to be available from Study ISEE2008 during the review of the NDA, these were not submitted in the NDA. The plan for submission of this was clarified via an Information Request and it was confirmed that these PK data from Study ISEE2008 will not be available during the review cycle for this NDA. The lack of availability of PK data from this study was not deemed to be an approvability issue from a clinical pharmacology perspective.

- Type B, Pre-NDA Meeting - May 27, 2022
    - Disssussed the the plan for Module 2.7.2, Summary of Clinical Pharmacology Studies

3.2 General Pharmacology and Pharmacokinetic Characteristics

The general pharmacology and pharmacokinetic characteristics of Avacincaptad pegol are summarized in **Table 2**.

Table 2. General Pharmacology and Pharmacokinetic Characteristics

	Avacincaptad pegol
Pharmacology	Avacincaptad pegol is an RNA aptamer, a PEGylated oligonucleotide that binds to and inhibits complement protein C5. By inhibiting C5, avacincaptad pegol prevents its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b [the initiating subunit of the membrane attack complex (MAC or C5b-9)] thus preventing MAC formation.
Dosing	2 mg (0.1 mL of 20 mg/mL solution) administered by IVT injection once monthly (approximately 28 ± 7 days).
Absorption	Mean free avacincaptad pegol plasma Cmax is estimated to be 68.4 ng/mL (57.8%) in nAMD patients. The observed Tmax was 7 days following single dose and predicted Tmax was 90 days following three monthly doses of 2 mg IVT injection. The predicted mean C_{max} of avacincaptad pegol at Month 1, 2, 3 and 12 for the 2 mg dose were 69.9, 82.0, 83.9 and 84.6 ng/mL, respectively. A minimal accumulation of avacincaptad pegol is expected in the vitreous or plasma following monthly repeat administration. The mean accumulation ratio at Month 12 based on predicted C_{min}, C_{max} and C_{ave} were 1.30, 1.36, and 1.42 respectively.
Distribution	With a C_{max} of 69.9 ng/mL after the first IVT injection based on PopPK analysis, the systemic exposure to avacincaptad pegol

	after the first dose is 7,000 times lower than that expected in the vitreous humor.
Metabolism/Elimination	Avacincaptad pegol is expected to be catabolized by endonucleases and exonucleases to oligonucleotides of shorter lengths which may be excreted renally, in similar manner to the elimination of endogenous RNA. The metabolism of avacincaptad pegol has not been fully characterized. The mean terminal half-life was estimated to be approximately 12 days.
Specific Populations	Following repeat monthly IVT dose administration of 2 mg avacincaptad pegol, no differences in the systemic PK of avacincaptad pegol were observed based on age, sex, and body weight based on population PK analysis. The effect of severe renal impairment or any degree of hepatic impairment on the PK of avacincaptad pegol is unknown. Significant increases in plasma avacincaptad pegol exposures are not expected with IVT route of administration.
Drug-drug Interaction	No studies evaluating the drug interaction potential of avacincaptad pegol have been conducted. RNA-based aptamers are not predicted to directly affect the hepatic, renal, or biliary elimination of other small molecules.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The clinical pharmacology information does not provide pivotal or supportive evidence of effectiveness of avacincaptad pegol. Since avacincaptad pegol is administered as IVT injection and the site of action is eye, the systematic exposure is not expected to affect treatment effect.

The efficacy of the proposed avacincaptad pegol dosing regimen in patients with GA secondary to AMD was evaluated in two independent, randomized, double-masked, sham-controlled pivotal studies in patients with GA (OPH2003 and ISEE2008). See clinical/statistical review for details regarding evidence of effectiveness for avacincaptad pegol.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed clinical dose of 2 mg administered by IVT injection once monthly is based on clinical efficacy and safety data obtained in two pivotal phase 3 multiple dose studies in patients with GA secondary to AMD (OPH2003, and ISEE2008).

In Study OPH2003, the 2 mg and 4 mg doses showed the greatest reduction in the GA area growth compared with sham. The reduction in mean GA area growth compared with sham in the 1 mg once monthly dose group was less than that observed for the 2 mg or 4 mg once monthly dose groups across study visits. In Study ISEE2008, the safety and efficacy of the 2 mg given once monthly were assessed comparing to sham. The results of the primary efficacy analyses in the two pivotal studies demonstrated the efficacy of Zimura for the treatment of GA secondary to AMD. Since avacincaptad pegol is intended for IVT injection and the site of action is eye, the systematic exposure is not expected to affect treatment effect. Therefore, exposure-efficacy or exposure-safety relationship was not evaluated. Refer to clinical and statistical review for additional safety and efficacy information for the proposed dosing regimen in the patient population.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

An alternate dosing regimen is not needed for any of the subpopulations. For the proposed drug product, the intended site of drug delivery and action is the eye; therefore, the extent of systemic exposure based on differences among subpopulations is not likely to influence the proposed drug product's efficacy. In addition, the information provided by the Applicant and assessment of the pharmacometrics (PM) aspects (see PopPK review in Appendix 4.2 for details) conclude that no clinically significant differences in the PK of avacincaptad pegol were observed based on age, sex, weight, and mild to moderate renal impairment.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

The drug product is given via IVT injection; therefore, the issue of a food-drug interaction is not relevant.

The potential for avacincaptad pegol to inhibit CYP450 enzymes was evaluated in vitro and based on the IC50 values (IC50 value were greater than 4 µM or 52 µg/mL) from this study and observed C_{max} of 68.4 ng/mL, it can be concluded that the DDI potential is low. In the invitro study, avacincaptad pegol was determined to be a weak inhibitor of CYP1A2 and CYP2D6. However, a clinical DDI is unlikely for the reasons described earlier regarding the many fold greater IC50 value in micromolar levels compared to low systemic levels of

avacincaptad pegol in humans with the TBM product. The C_{max}/Ki ratio for CYP1A2 and CYP2D6 was 0.0012, indicating that a CYP-mediated DDI is unlikely. No clinical drug interaction studies were conducted for avacincaptad pegol, which is acceptable.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Avacincaptad pegol concentrations in human plasma were measured using a colorimetric hybridization assay with a lower limit of quantitation (LLOQ) of 3.4 ng/mL and an upper limit of quantitation (ULOQ) of 120 ng/mL. The analytical method validation and performance are deemed acceptable.

The sample preparation, stability, analysis accuracy, and precision, and other relevant bioanalytical method aspects for relevant clinical pharmacology study were reviewed by the Clinical Pharmacology reviewer and are deemed to be acceptable. The method validation and performance results can be seen in **Table 3** and **Table 4**, respectively.

Table 3. Bioanalytical Method Validation of Avacincaptad pegol

	Validation of the Dual Probe Hybridization Assay for the Measurement of Avacincaptad Pegol in Human K_2EDTA Plasma
Report Number	QPS# 259-0703
Test Article	Avacincaptad pegol (ARC1905)
Analytical Method Type	Oligonucleotide Hybridization Assay
Biological Matrix	Human plasma
Anticoagulant	EDTA
Calibrator Range	2.0 to 120.0 ng/mL
QC Samples	10.0, 50.0, and 100.0 ng/mL
LLOQ	3.4 ng/mL
ULOQ	120 ng/mL
Requirement/Parameter	**Data Summary**
Calibration Standards	Acceptance criteria of ≤ 20% were met
4-Parameter Logistic Regression Model	Mean %CV ≤ 20% and %RE ± 20%
Precision and Accuracy	Acceptance criteria of ≤ 20% were met
Matrix Evaluation	Acceptance criteria were met (all avacincaptad pegol concentrations < 3.4 ng/mL)
Selectivity Evaluation	Acceptance criteria were met, with > 80% of the matrix lots passing
Linearity of Dilution and Hook Effect	Linearity of dilution of avacincaptad pegol was up to 50,000-fold with a reported hook effect at 400,000 ng/mL. Precision across the dilution range was 1.5%
Bench-Top Stability	17 hours at ambient temperature
Freeze-Thaw Stability	Acceptance criteria were met for three freeze-thaw cycles between -80°C and ambient temperature
Stock Solution Stability	257 days at -20°C for 5 mg/mL in 0.9% saline
Long-Term Storage Stability	91 days at -80°C of ARC1905 (10 ng/mL and 100 ng/mL) in human plasma

Source: Module 2.7.1 of NDA 217225, Page 11, Table 2.7.1.1-5
%CV = percentage of coefficient of variation; %RE = percentage of relative error; EDTA = ethylenediaminetetraacetic acid; K2EDTA = dipotassium EDTA; LLOQ = lower limit of quantification; QC = quality control; ULOQ = upper limit of quantification.

Table 4. Bioanlaytical Method Performance of Avacincaptad pegol

Assay passing rate	Of the 45 incurred samples re-analyzed, 9 (20%) were observed to have a percent difference >30% compared to their original reported value
Standard curve performance	Cumulative bias range (%RE): -14 to 9.8 Cumulative precision (%CV): 1.1 to 20.7
QC performance	Cumulative bias range (%RE): -4.7 to 9.8 LQC: 9.8 MQC: - 2.0 HQC: - 4.7 Cumulative precision (%CV): 7.8 to 10.1 LQC: 10.1 MQC: 7.9 HQC: 7.8
Method reproducibility	Incurred sample re-analysis was performed in 12% of study samples, and 80% of the samples met the pre-specified criteria.
Study sample analysis/ stability	Stock solution stability is 257 days at -20°C for 5 mg/mL in 0.9% saline % Difference with Day1: -2.4 for 10 ng/mL sample -10.9 for 100 ng/mL sample
Standard calibration curve performance during accuracy and precision runs	Eight standard calibrators from LLOQ (3.4 ng/mL) to ULOQ (120 ng/mL). Bias Range (%RE): -14 to 9.8 Accuracy Range (%CV): 1.1 to 20.7

Source: Module 2.7.1 of NDA 217225, Page 17, Adapted from Table 2.7.1.4-2
%CV = percentage of coefficient of variation; %RE = percentage of relative error; HQC = higher quality control; LLOQ = lower limit of quantification; LQC = lower quality control; MQC = middle-quality control; QC = quality control; ULOQ = upper limit of quantification.

4.2 Population PK Analyses

The goal of the population PK (Pop PK) analysis was to develop a Pop PK model to perform Pop PK analysis of avacincaptad pegol in plasma following IVT injection in AMD patients and assess sources of intrinsic and extrinsic variability. Also, simulations were performed to determine steady state exposure and the extent of accumulation of avacincaptad pegol following repeated once monthly dosing.

The Pop PK model included 1 clinical trial, OPH2000. The baseline population characteristics in the PopPK model evaluation dataset is provided in **Table 5**. The Pop PK analysis was conducted by the Applicant and the final Pop PK model was a one-compartment PK model with first-order rate constant of absorption (Ka). A variance component characterizing between-subjects variability (BSV) in model parameters was included, and residual unexplained variability was

modeled using additive, proportional or additive and proportional models.

Dataset preparation, exploration and graphs was performed using R® Version 4.0 or higher. Population PK modeling was performed using NONMEM® Version 7.3 or higher.

Because of the low systemic exposure of avacincaptad pegol, 39.9% of the PK samples had undetectable concentrations of avacincaptad pegol. Based on the expected low systemic exposure, different approaches for handling BLQ data were considered in order to reduce estimation bias and optimally characterize the terminal elimination half-life of avacincaptad pegol. The method M3 suggested by Beal is based on simultaneous modeling of continuous and categorical data where the BLQ observations are treated as categorical data. Thus, the base model was customized by including the likelihood method (M3) to account for the probability of undetectable concentrations of avacincaptad pegol over time.

The goodness of fit plot and visual predictive checks (VPC) can be seen in **Figure 1** and **Figure 2**, respectively.

Table 5. Baseline Population Characteristics in the PopPK Model Evaluation Dataset – Categorical Data

Characteristics	Overall (N=60)
Sex	
Female	42 (70.0%)
Male	18 (30.0%)
Race	
White	60 (100%)
Black or African American	0 (0%)
Asian	0 (0%)
American Indian or Alaska Native	0 (0%)
Native Hawaiian or Other Pacific Islander	0 (0%)
Multiple	0 (0%)
Other	0 (0%)
Not Collected	0 (0%)
Ethnicity	
Hispanic or Latino	0 (0%)
Not Hispanic or Latino	60 (100%)
Hepatic Function Category	
Normal Hepatic Function	59 (98.3%)
Mild B1 Hepatic Impairment	1 (1.7%)
Mild B2 Hepatic Impairment	0 (0%)
Moderate Hepatic Impairment	0 (0%)
Severe Hepatic Impairment	0 (0%)
Renal Impairment Category	
Normal Renal Function	4 (6.7%)
Mild Renal Impairment	23 (38.3%)
Moderate Renal Impairment	31 (51.7%)
Severe Renal Impairment	2 (3.3%)

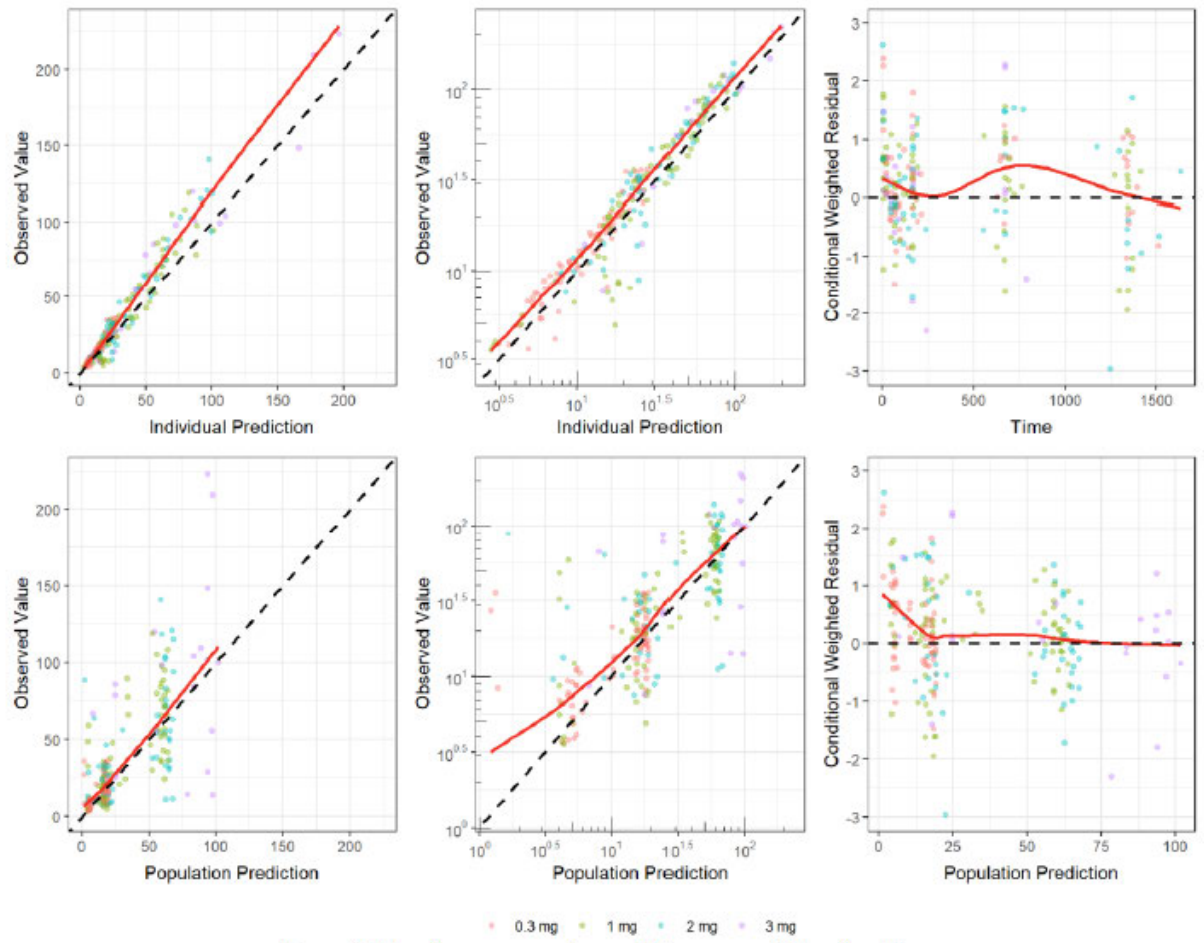
Normal renal function (CLcr ≥ 90 mL/min/1.73m^2), mild renal impairment (CLcr ≥ 60 to 89 mL/min/1.73m^2), moderate renal impairment (CLcr ≥ 30 to 59 mL/min/1.73m^2), severe renal impairment (CLcr 15 to 30 mL/min/1.73m^2).

Characteristics	Overall (N=60)
Age (years)	
Mean (SD)	77.7 (7.34)
Median [Min, Max]	80.0 [54.0, 90.0]
Body Weight (kg)	
Mean (SD)	71.4 (12.2)
Median [Min, Max]	71.4 [48.0, 97.1]
Height (cm)	
Mean (SD)	163 (7.03)
Median [Min, Max]	165 [150, 176]
Body Surface Area (m^2)	
Mean (SD)	1.77 (0.166)
Median [Min, Max]	1.78 [1.48, 2.09]
Body Mass Index (kg/m^2)	
Mean (SD)	26.7 (3.87)
Median [Min, Max]	27.1 [17.6, 35.2]
Alkaline Phosphatase (U/L)	
Mean (SD)	75.5 (22.0)
Median [Min, Max]	70.0 [41.0, 143]
Alanine Aminotransferase (U/L)	
Mean (SD)	15.1 (5.87)
Median [Min, Max]	14.0 [6.00, 38.0]
Aspartate Aminotransferase (U/L)	
Mean (SD)	21.8 (8.29)
Median [Min, Max]	20.5 [13.0, 67.0]
Bilirubin (mg/dL)	
Mean (SD)	0.541 (0.221)
Median [Min, Max]	0.468 [0.176, 1.29]
Creatinine (mg/dL)	
Mean (SD)	0.973 (0.203)
Median [Min, Max]	0.904 [0.678, 1.50]
Creatinine Clearance (mL/min)	
Mean (SD)	59.4 (19.1)
Median [Min, Max]	56.6 [26.9, 126]
eGFR	
Mean (SD)	72.8 (20.2)
Median [Min, Max]	70.6 [33.1, 112]

ALT = alanine transferase; AST = aspartate aminotransferase; BMI = body mass index; BSA = body surface area; eGFR = estimated glomerular filtration rate.

Source: Applicant's popPK report, Pages 17-18, Table 1-2

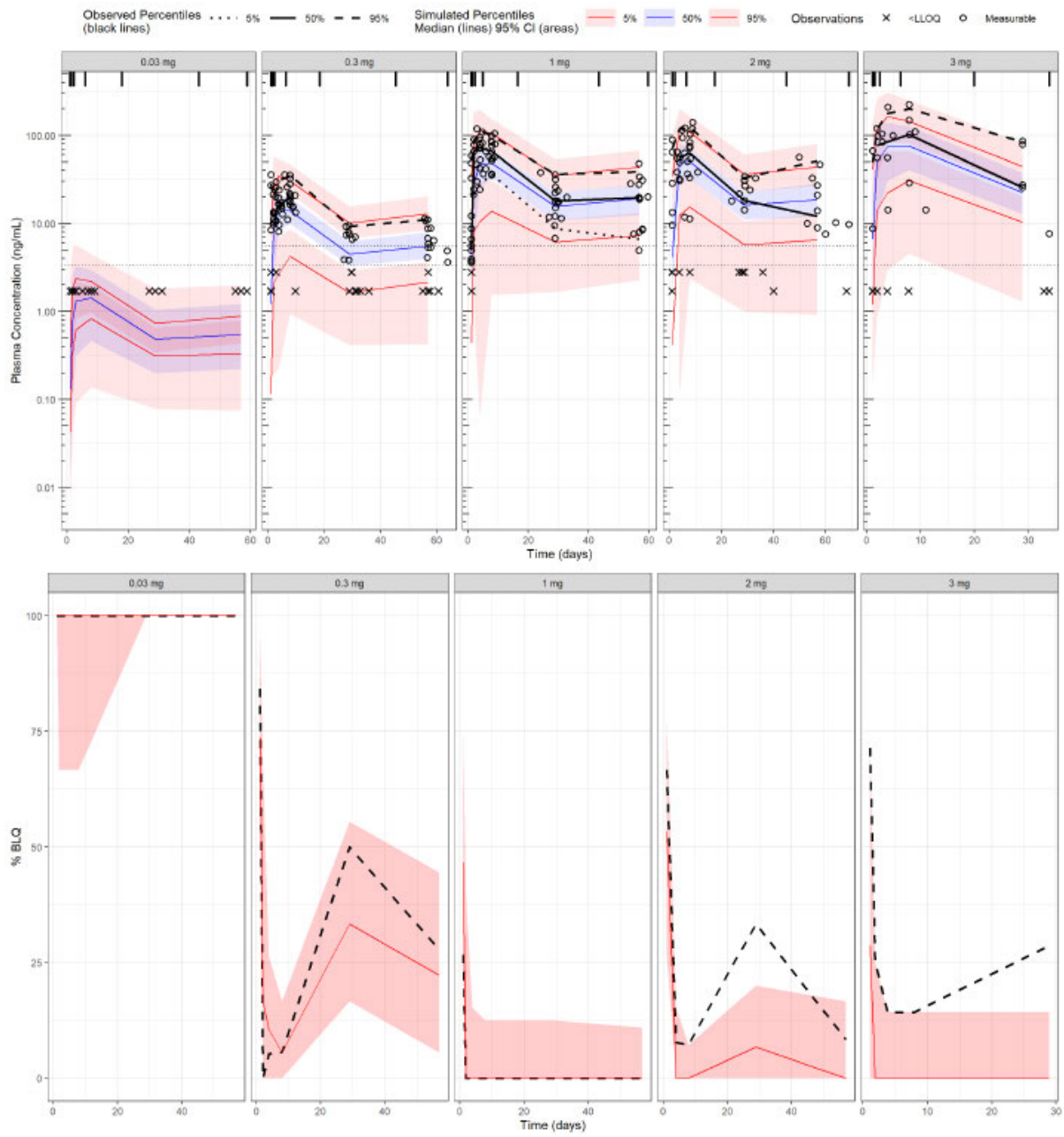
Figure 1. Goodness of Fit Plots of the Final PopPK Model: Population and Individual Predicted vs. Observed Concentrations of Avacincaptad Pegol



Legend: blue line = regression; red line = smoothing function

Source: Applicant's popPK report, Page 23, Figure 2

Figure 2. Visual Predictive Checks of Final Population PK Model



Source: Applicant's popPK report, Page 24, Figure 3

The influence of continuous and categorical covariates was tested for their statistically significant impact on the PK parameters in the model. Covariates were selected based on known or hypothetical factors that could affect the PK. These covariates include dose, age, body weight, sex, creatinine clearance and degree of renal impairment. Selected covariates were formally tested using a forward addition process followed by a backward deletion process. Parameter estimates of final popoulation PK model are provided in **Table 6**.

Table 6. Population PK Analysis of Avacincaptad Pegol: Parameter Estimates

Parameter	Estimate (RSE)	BSV (RSE)	Shrinkage	Bootstrap Estimate (RSE)
CL/F (L/h)	0.0321 (0%)	NA	NA	0.0317 (3.27%)
V/F (L)	1.29 (3.70%)	301.2% (0.05%)	7.5%	1.25 (11.6%)
Ka (h^{-1})	0.00269 (3.40%)	NA	NA	0.00269 (3.10%)
Frel (Fraction)	1, Fixed (NA) × (1-0.47) if Dose ≥ 2 mg (0%)	37.6% (0.05%)	18.4%	1, Fixed (NA) × (1 - 0.463) if Dose ≥ 2 mg (8.87%)
Error Model	Proportional: 0.394 (0.2%)	NA	NA	0.396 (5.73%)

Source: Applicant's popPK report, Table 5, Page 22

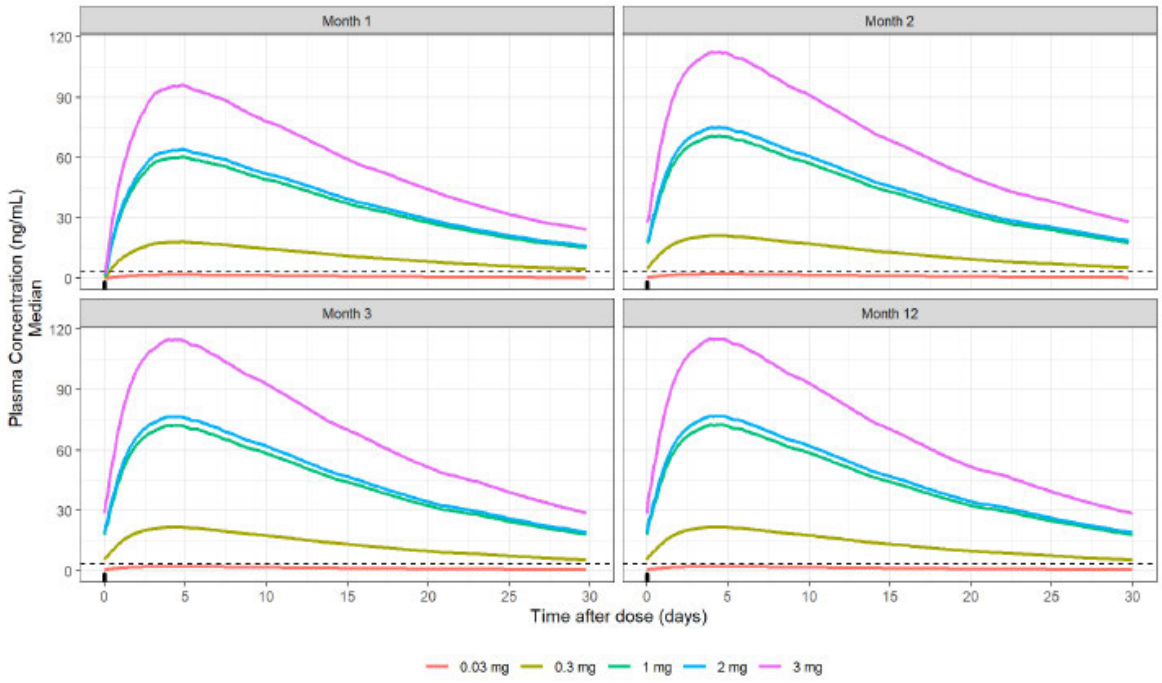
CL/F = apparent clearance, V/F = apparent volume of distribution; Ka = rate constant of absorption; Frel = relative bioavailability; BSV = between- subject variability; RSE = relative standard error.

Based on a covariate analysis, the effect of dose on the absorption of avacincaptad pegol was statistically significant while other covariates such as age, body weight, sex, creatinine clearance and renal impairment (mild, moderate and severe) were not statistically significant. The effect of dose on F_{rel} for dose levels ≥2 mg was -0.47, suggesting that the transfer of avacincaptad pegol from the vitreous humor to the bloodstream was reduced by 47%. For example, typical subjects receiving 2 and 3 mg doses would be expected to present systemic exposure equivalent to 1.06 and 1.59 mg doses, respectively. The effect of dose is likely attributed to the higher injection volume for the 2 and 3 mg dose levels (0.10 mL) as opposed the 0.03, 0.3 and 1 mg dose levels (0.05 mL).

Reviewer comment: Overall, the final model reasonably well described the systematic observation of avacincaptad pegol. The statistically significant effect of dose on Frel suggests transfer of avacincaptad pegol from the vitreous humor to the bloodstream is likely to be reducted. This effect is not considered clinically relevant as the proposed dose is fixed 2 mg for all patients.

Based on the final population PK model, individual Bayesian estimates of PK parameters were used to predict rich concentration-time profiles of avacincaptad pegol following once monthly dosing for 12 months. Mean concentration-time profiles at Month 1, 2, 3, and 12 for each dose levels are presented on linear scale and can be seen in **Figure 3**.

Figure 3. Mean Concentration-Time Profiles of Avacincaptad Pegol at Month 1, 2 and 12 for Each Dose Level



Source: Applicant's popPK report, Figure 4, Page 25

The mean C_{max} of avacincaptad pegol at Month 1, 2, 3 and 12 for the 2 mg dose were 69.9, 82.0, 83.9 and 84.6 ng/mL, respectively. The C_{max} at Month 3 was approximately 99% that observed at Month 12. Overall, maximum plasma concentrations are predicted to be reached within 90 days (Month 3) after monthly IVT administration of avacincaptad pegol 2 mg consistent with a mean terminal half-life of approximately 12 days. The mean accumulation ratio at Month 12 based on C_{min}, C_{max} and C_{ave} were 1.30, 1.36 and 1.42 , respectively.

Reviewer comment:

Given a C_{max} of 69.9 ng/mL after the first injection, applicant claims the systemic exposure to avacincaptad pegol after the first dose is 7,000 times lower than that expected in the vitreous humor. This was based on the assumption that homogeneous distribution in a vitreous volume of 4 mL (i.e., 2000 µg / 4 mL) will result in the C_{max} of avacincaptad pegol in the vitreous humor at about 500 µg/mL immediately after the first injection. The Pop PK analysis performed by the Applicant appears reasonable to support the labeling claims made by Applicant regarding no differences in systemic PK of avacincaptad pegol based on age, sex, and body weight. Thus, there is no need for dose adjustment for any of the populations that have been studied with regards to age, sex, and body weight. The effect of severe renal impairment or any degree of

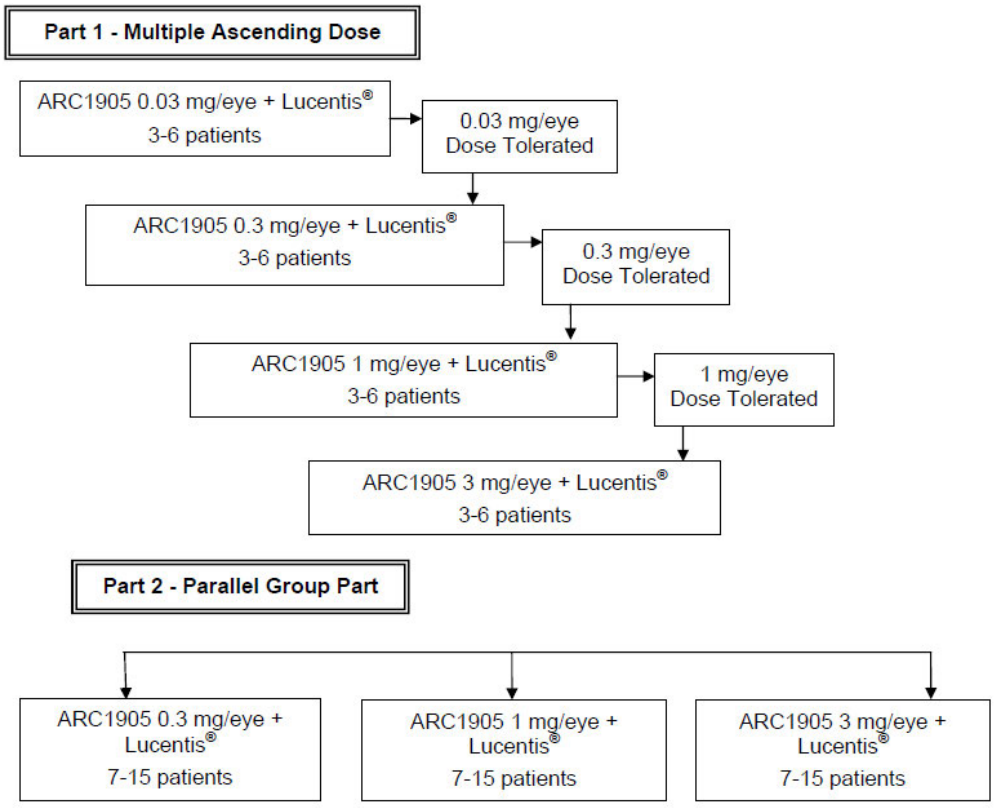
hepatic impairment on the PK of avacincaptad pegol is unknown. As significant increases in plasma avacincaptad pegol exposures are not expected with IVT route of administration, no dosage adjustment is needed based on renal or hepatic impairment status.

4.3 Study OPH2000 Individual Study Review

This was a first-in-human, two-part Phase 1 ascending multiple-dose open- label study where 60 patients were enrolled. The study design can be seen in **Figure 4**.

Figure 4. Study OPH2000 Design Schematic

Following Protocol Amendment D, a fourth dose level (2 mg/eye) was added to replace the 3 mg/eye dose level.



Source: Study OPH2000 CSR, Figure 1, Page 23

In Part 1, of the MAD study, patients were assigned to one of four avacincaptad pegol dose groups: 0.03, 0.3, 1, or 3 mg. The injection volumes were 0.05 mL for the avacincaptad pegol 0.03 mg, 0.3 mg, and 1 mg doses and 0.1 mL for the avacincaptad pegol 3 mg dose. Patients received Lucentis (0.5 mg) followed by avacincaptad pegol on the same day for three dose administrations at four-week intervals, with follow-up visits at Week 12 and Week 24. Patients who were consented to Protocol Amendment C on or before the Week 12 visit received three additional doses of Lucentis (0.5 mg) followed by avacincaptad pegol at Weeks 12, 16, and 20,

with a follow-up visit at Week 24. Each dose group was enrolled in an escalating fashion once the third patient at each dose level completed a safety period of one week after their first dose of avacincaptad pegol, including visits at Day 1, Day 3, and Week 1. Venous blood samples for PK analysis were collected at 0 (pre-dose), 4, 24, 48, and 168 hours after administration of the first dose and pre-dose prior to the Week 4 and Week 8 IVT injections.

In Part 2, the parallel group portion of the study, new patients were originally assigned to receive one of three doses of avacincaptad pegol: 0.3, 1, or 3 mg. Patients from Part 1 treated at the corresponding dose levels in Part 1 also contributed towards the total enrollment in each combination therapy cohort in Part 2. As also done in part 1 of the study, due to a drug stability issue with the 3 mg dose (possible dimerization of the aptamer), active patients in Part 2 originally assigned to the avacincaptad pegol 3 mg dose transitioned to the 1 mg dose group under Protocol Amendment D. No additional patients were enrolled in the 3 mg dose group. Also, at this time, an additional avacincaptad pegol dose group, 2 mg, was introduced.

Patients received Lucentis (0.5 mg) followed by avacincaptad pegol on the same day for three dose administrations at four-week intervals, with follow-up visits at Week 12 and Week 24. As was done in Part 1, patients who were consented to Protocol Amendment C on or before the Week 12 visit received three additional doses of Lucentis (0.5 mg) followed by avacincaptad pegol at Weeks 12, 16, and 20, with a follow-up visit at Week 24. Venous blood samples for PK analysis in Part 2 were collected according to the same PK sampling scheme used in Part 1.

The PK samples were analyzed for avacincaptad pegol concentrations using a colorimetric hybridization assay with a lower limit of quantitation (LLOQ) of 3.4 ng/mL and an upper limit of quantitation (ULOQ) of 120 ng/mL. The bioanalytical method is deemed to be acceptable as can be seen in Section 4.1 of this review.

The PK parameters can be seen in **Table 7**. Avacincaptad pegol plasma concentrations were not detectable in any patients receiving avacincaptad pegol 0.03 mg. Plasma area under the curve $AUC_{0-\infty}$ and C_{max} increased with increasing avacincaptad pegol dose from 0.3 mg to 3.0 mg with the only exception being the similar C_{max} of the 1 mg and 2 mg doses. Median time to maximum concentration (T_{max}) values ranged from 5.4 days to 6.9 days. There was no meaningful accumulation of avacincaptad pegol in plasma following two avacincaptad pegol dose administrations given once a month (based on the mean pre-dose concentrations of 16.7 and 20.3 ng/mL prior to the 2nd and 3rd doses at Weeks 4 and 8 respectively).

The C_{max} and $AUC_{0-\infty}$ of the avacincaptad pegol 1 mg dose were dose-proportional to the 0.3 mg dose, whereas the C_{max} and $AUC_{0-\infty}$ of the 2 mg and 3 mg doses were less than dose-proportional to the 0.3 mg dose.

Table 7. Summary of PK Parameters from Study OPH2000

Study	Indication	Study Design/ Study Objective	Number of Patients	Age Range (Years)	IVT Dose	Mean Pharmacokinetic Parameters (CV%)			
						C_{max} (ng/ml)	t_{max} (day)[a]	$AUC_{0-\infty}$ (h•ng/mL)	AUC_{0-t} (h•ng/mL)
OPH2000	nAMD	Phase 1 multicenter, open-label ascending dose (Part 1), parallel group (Part 2) clinical trial to establish the safety, tolerability, and pharmacokinetic profile of multiple IVT injections of avacincaptad pegol given in combination with multiple doses of Lucentis 0.5 mg	3	72-82	0.03 mg	NC	NC	NC	NC
			19	54-86	0.3 mg	21.9 (35.9)	6.8 (0.1-8.9)	518.5 (26.4)	233 (69.4)
			16	56-90	1 mg	73.1 (34.4)	5.4 (1.9-7.9)	1589 (34.2)	1164.1 (29.0)
			15	68-88	2 mg	68.4 (57.8)	6.8 (0.2-9.9)	1948.4 (27.9)	999.9 (71.9)
			7	71-87	3/1 mg[b]	97.3 (75.0)	6.9 (2.8-9.9)	3349.6 (72.6)	1643.4 (96.5)

Source: Module 2.7.2, Table 2.7.2.2-1, Page 15

AUC = area under curve; Cmax = maximum concentration; CV = coefficient of variation; GA = geographic atrophy; IVT = intravitreal; nAMD = neovascular age-related macular degeneration; NC = not calculated; tmax = time to maximum concentration

[a] tmax is reported as median (minimum – maximum).

[b] Under Protocol Amendment D, the active patients in Part 2 originally assigned to 3 mg transitioned to the 1 mg dose group due to a drug stability issue with the 3 mg dose. Note: Avacincaptad pegol plasma concentrations were below the limit of detection in all patients receiving 0.03 mg dose. Thus, PK parameter were not analyzed.

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