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Population Pharmacokinetics of Pegcetacoplan in Patients with Geographic Atrophy or Neovascular Age-related Macular Degeneration

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Objective: To develop a population pharmacokinetic (PK) model to characterize serum pegcetacoplan concentration-time data after intravitreal administration in patients with geographic atrophy (GA) or neovascular age-related macular degeneration (nAMD).

Design: Pharmacokinetic modeling.

Participants: Two hundred sixty-one patients with GA or nAMD enrolled in 4 clinical studies of pegcetacoplan.

Methods: Serum concentration data were pooled from 4 clinical studies. Pegcetacoplan dosing included single intravitreal injections of 4, 10, and 20 mg and multiple intravitreal injections of 15 mg monthly or every other month. Considering a high proportion of samples were below the limit of quantification (BLQ) in serum following intravitreal administration, the M3 method of likelihood-based handling of data BLQ was employed in NONMEM (version 7.4). Covariate model development was performed using stepwise forward ($\alpha = 0.05$) and backward ($\alpha = 0.001$) selection. Predicted PK parameters and exposure metrics were generated via simulation in serum and vitreous humor.

Main Outcome Measures: Pharmacokinetic parameters.

Results: Intravitreal pegcetacoplan displayed absorption-limited (i.e., "flip-flop") kinetics with median empirical Bayes estimated pegcetacoplan absorption and elimination half-lives of 13.1 days and 4.51 days, respectively. Vitreous exposure was predicted to be >1300-fold higher than serum exposure, with maximum concentrations in serum below the threshold required to elicit systemic pharmacodynamic effects. Drug accumulation from first dose to steady state was predicted to be minimal in serum (mean accumulation ratio = 1.50 with monthly dosing, 1.10 with every-other-month dosing) and vitreous humor (mean accumulation ratio = 1.30 with monthly dosing, 1.10 with every-other-month dosing). Age, sex, and baseline C3 level were identified as significant ($P < 0.001$) predictors of apparent serum pegcetacoplan clearance after intravitreal administration; however, none of the covariate effects appeared to be clinically meaningful given the low absolute maximum serum concentrations achieved (<5 μg/mL). Concomitant anti-VEGF treatment did not significantly influence vitreous disposition of pegcetacoplan as assessed in a dedicated post hoc covariate model.

Conclusions: This population PK model adequately described the serum concentration-time profile of pegcetacoplan after intravitreal administration in adults with GA or nAMD.

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Age-related macular degeneration (AMD), a complex progressing retinal disease, is the leading cause of irreversible blindness in adults >75 years old, particularly in the United States and other Western countries.[1,2] The advanced form of dry AMD, referred to as geographic atrophy (GA), is characterized by sharply demarcated atrophic lesions of the outer retina.[3,4] Geographic atrophy has an estimated prevalence of 5 million patients globally and 1 million in the United States.[5] It profoundly affects patient functioning, including activities of daily living, driving, reading, work schedules, social activities, facial recognition, and mental health.[6]

The cause of AMD and its progression to GA remains unknown; however, overactivation of the complement system has been hypothesized to be an underlying factor.[3] This is supported by evidence that genetic variants of complement factors increase susceptibility to AMD.[3] Complement activation products were identified at elevated levels in plasma and deposited in ocular tissues of patients with AMD.[7] The complement activation

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products were most notably reported in drusen, which are yellow lipoprotein deposits that accumulate between the retinal pigment epithelium and Bruch's membrane in early to intermediate AMD stages.[3,7]

Pegcetacoplan, a pegylated peptide complement C3 inhibitor, is the first drug approved by the United States Food and Drug Administration for treating GA.[3,7] By inhibiting complement activation through binding of complement proteins C3 and C3b,[8,9] pegcetacoplan is hypothesized to prevent continuing C3 deposition and phagocytosis, thereby enabling cell survival.[7] Viable endothelium in the choriocapillaris, adjacent to areas of GA, may then regrow new vessels.[7] Treatment with pegcetacoplan led to significant reductions in the rate of GA lesion growth over 12 months in the phase II FILLY study and over 24 months in the combined analysis of subsequent phase III DERBY and OAKS studies.[7,9] An increase in the pegcetacoplan treatment effect was noted in phase III studies between months 18 and 24 compared with the previous 6-month periods.[9] Given the inaccessibility of relevant ocular matrices, a population modeling approach was used to support inference on ocular exposure to pegcetacoplan based on observations in serum. This strategy has been employed in the development of drug products for intravitreal administration to treat ophthalmic diseases, including pegylated molecules.[10–12] A population pharmacokinetic (PK) model allows the prediction of exposure at the site of action in the vitreous space, which can be used as an input in modeling patient response to treatment as well as the assessment of intrinsic and extrinsic patient factors (i.e., covariates) on exposure to evaluate the need for altered posology in specific patient populations.

This analysis was conducted to develop a population PK model to characterize the serum pegcetacoplan concentration-time data after intravitreal administration in patients with GA or neovascular AMD (nAMD), including assessment of clinically relevant covariates on pegcetacoplan PK parameters, to derive a final predictive PK model for intravitreal administration.

Methods

Model Data

This population PK analysis was conducted using serum drug concentration data after intravitreal administration of pegcetacoplan in 4 clinical studies (studies POT-CP043014, APL2-203, POT-CP121614 [FILLY], and APL2-303 [DERBY]). This study was conducted in accordance with the principles of the Declaration of Helsinki, and all participants provided written informed consent prior to enrollment. The protocols and informed consent forms were approved by the institutional review board for each study center.

Dosing included pegcetacoplan single intravitreal injections of 4, 10, and 20 mg and multiple intravitreal injections of 15 mg monthly or every other month in patients with GA or nAMD. Given that the proportion of PK samples below the limit of quantification (BLQ) in serum after intravitreal administration was >20%, the M3 method of likelihood-based handling of data was used in NONMEM (version 7.4).[13] The lower limit of quantification for pegcetacoplan in serum was 0.10 μg/mL.

Model Development

The final structural model was composed of 2 compartments: a vitreous dose administration compartment and a serum systemic disposition compartment (Fig 1). The parameters included in the model were vitreous-to-serum absorption rate constant (KA), systemic bioavailability, clearance (CL), and volume of the central compartment (VC). Both KA and systemic elimination from serum were modeled as first-order processes. Pegcetacoplan, administered intravitreally, was anticipated to be eliminated entirely via absorption into systemic circulation; therefore, systemic bioavailability was assumed to be 1, and systemic parameters (CL and VC) were interpreted as apparent values (CL/F and VC/F). For this model, vitreous volume was assumed to be 4 mL for generation of vitreous exposure predictions based on consensus reports from early postmortem studies.[14]

Model Parameterization

Parameter estimation used first-order conditional estimation and second-order approximation with interaction (FOCE + I LAPLACE) in NONMEM version 7.4. A log-transform both sides approach was used in which the dependent variable in the analysis was log-transformed serum pegcetacoplan concentration and fixed effects were parameterized using a log-transformation. Skewedness in the interindividual variability of apparent systemic CL from serum (CL/F) was accounted for using a Manly transformation.[15]

Covariate Parameterization

Covariates were evaluated using stepwise forward selection and backward elimination. Covariates evaluated included (1) disease type (GA vs. nAMD), sex, age, baseline serum C3, baseline total bilirubin, baseline serum albumin, baseline alanine aminotransferase, baseline aspartate aminotransferase, and estimated glomerular filtration rate versus CL/F; (2) disease type, sex, baseline serum C3, and baseline serum albumin versus VC/F; and (3) disease type, sex, formulation, and age versus KA.

Model Evaluation

Models were evaluated using prediction-corrected concentration-time and fraction BLQ visual predictive checks.[16]

Model Applications

Exposure Predictions

The model was used to simulate individual concentration-time profiles from which exposure metrics were calculated

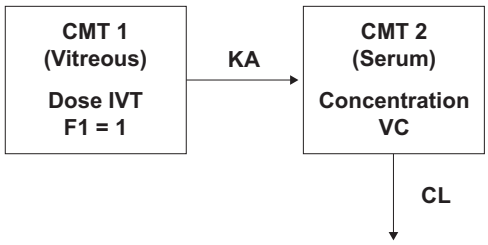

Figure 1. Population PK model structure. CL = clearance; CMT = compartment; F1 = bioavailability; IVT = intravitreal; KA = absorption rate constant; PK = pharmacokinetics; VC = volume of central compartment.

for serum and vitreous humor in a GA population. A total of 1000 virtual patients were generated by sampling complete covariate vectors from patients in the observed data set with replacement to retain correlation between covariates in the simulations. Individual predicted PK parameters and concentration-time profiles were generated over the first dosing interval and at steady-state for pegcetacoplan 15 mg monthly and every-other-month dosing regimens.

Forest Plots

The impact of covariate effects was illustrated using forest plots. Parameter estimation uncertainty was incorporated using a parametric bootstrapping procedure with the multivariate normal distribution as an approximate posterior distribution. An input simulation data set was created with individual patients differing in only one covariate value from the reference patient and dosing records for pegcetacoplan 15 mg monthly dosing sufficient to reach steady-state. A total of 1000 simulation output data sets were generated using 1000 unique sets of model parameters containing steady-state pegcetacoplan exposure.

Anti-VEGF Post Hoc Model

An anti-VEGF post hoc model was generated by adding the following covariate-parameter relationships to the final model: anti-VEGF on CL/F, anti-VEGF on VC/F, and anti-VEGF on KA.

Results

Study Population

A total of 2064 PK samples were collected from 261 patients enrolled in studies POT-CP043014 (n = 13, nAMD), APL2-203 (n = 17, nAMD), POT-CP121614 (n = 164, GA), and APL2-303 (n = 67, GA) after the first dose of pegcetacoplan. Of the 2064 PK samples, 1581 (76.6%) were quantifiable and 483 (23.4%) were BLQ. At baseline, the mean age (standard deviation) of patients was 79.6 (7.69) years, 56.7% (n = 148) were female, and mean C3 (standard deviation) was 1.20 (0.241) g/L (Table 1). Most patients had GA (n = 231; 88.5%), were White (n = 254; 97.3%), and had mild to moderate renal impairment (n = 193; 73.9%).

PK Parameters

The PK parameters in the final model were based on the typical patient with GA or nAMD: male, 80 years of age, and with baseline C3 1.2 g/L. The model-predicted parameters after intravitreal administration of pegcetacoplan included KA of 0.0528 $days^{-1}$, VC/F of 1.83 L, and CL/F of 0.325 L/day (Table 2). Pegcetacoplan displayed absorption-limited kinetics with a geometric mean vitreous-to-serum absorption half-life of 13.1 days and a serum elimination half-life of 4.51 days. The mean maximum (peak) concentration (C_{max}) was predicted to be 2.20 µg/mL (25.9% coefficient of variation) and 1.50 µg/mL (46.1% coefficient of variation) at doses of 15 mg monthly and 15 mg every other month, respectively. The average steady-state exposure over the dosing interval was approximately twofold higher in the vitreous compartment with monthly versus every-other-month dosing (geometric mean: 2409 µg/mL with monthly dosing, 1229 µg/mL with every-other-month dosing). Drug accumulation from first dose to steady-state was predicted to be minimal in both serum (mean accumulation ratio = 1.50 with monthly dosing, 1.10 with every-other-month dosing) and vitreous humor (mean accumulation ratio = 1.30 with monthly dosing, 1.10 with every-other-month dosing) (Table 3). Vitreous exposure was predicted to be >1300-fold higher than serum exposure by ratio of steady-state area under the curve (AUC), while serum exposure was predicted to be below the level required for systemic pharmacodynamic effects (vitreous humor geometric mean AUC was 72 266 µg/mL•day with monthly dosing and 73 758 µg/mL•day and with every-other-month dosing; serum geometric mean AUC was 50.8 µg/mL•day with monthly dosing and 46.2 µg/mL•day with every-other-month dosing).

Covariate Effects

Age, sex, and baseline serum C3 levels were identified by forward and backward selection as covariates of pegcetacoplan CL/F after intravitreal administration (Fig 2). Female patients were predicted to have a larger impact (1.26-fold increase; 90% confidence interval [CI]: 1.21, 1.32) in steady-state serum C_{max} than male patients. Age and baseline C3 were not predicted to result in exposure beyond 0.8- to 1.25-fold of reference over the range of values representing 90% of individuals in the analysis. None of these covariate effects were anticipated to be clinically meaningful considering the low absolute maximum serum concentrations (<5 µg/mL) achieved across conditions and lack of a predicted impact on vitreous exposure. Concomitant anti-VEGF treatment was predicted to result in a modest reduction in serum exposure compared with no concomitant treatment, with 90% CIs for AUC and C_{max} including the lower bound of the ratio reference range of 0.8 (Fig 3). However, vitreous exposure is not anticipated to be affected by concomitant use of anti-VEGF medications based on a 95% CI for the multiplicative effect of these concomitant medications on KA including the null value of 1 (95% CI: 0.980, 1.37).

Discussion

This is the first study to report a population PK model for pegcetacoplan after intravitreal administration and model-predicted PK parameters in vitreous humor. The ocular disposition of pegcetacoplan after intravitreal administration was inferred from analysis of serum concentration-time data. The predicted PK parameters suggest pegcetacoplan disposition is absorption limited after intravitreal administration, displaying a "flip-flop" kinetic profile wherein vitreous-to-serum absorption is slower than elimination. Correspondingly, the median empirical Bayes estimated pegcetacoplan absorption half-life of 13.1 days is longer than the estimated elimination half-life of 4.51 days, further

Table 1. Baseline Characteristics of Study Population

Characteristic	Study POT-CP043014 (n = 13)	Study POT-CP121614 (n = 164)	Study APL2-203 (n = 17)	Study APL2-303 (n = 67)	Total (n = 261)
Age, mean (SD), yrs	74.5 (8.02)	80.3 (7.55)	77.2 (8.76)	79.3 (7.32)	79.6 (7.69)
Disease type, n (%)					
GA	0 (0)	164 (100)	0 (0)	67 (100)	231 (88.5)
nAMD	13 (100)	0 (0)	17 (100)	0 (0)	30 (11.5)
Sex, n (%)					
Male	5 (38.5)	60 (36.6)	10 (58.8)	38 (56.7)	113 (43.3)
Female	8 (61.5)	104 (63.4)	7 (41.2)	29 (43.3)	148 (56.7)
Race, n (%)					
White	13 (100)	159 (97.0)	16 (94.1)	66 (98.5)	254 (97.3)
Black	0 (0)	2 (1.2)	0 (0)	0 (0)	2 (0.8)
Other or missing	0 (0)	3 (1.8)	1 (5.9)	1 (1.5)	5 (1.9)
Renal impairment					
Normal	4 (30.8)	37 (22.6)	4 (23.5)	6 (9.0)	51 (19.5)
Mild	7 (53.8)	70 (42.7)	9 (52.9)	26 (38.8)	112 (42.9)
Moderate	2 (15.4)	45 (27.4)	3 (17.6)	31 (46.3)	81 (31.0)
Severe	0 (0)	2 (1.2)	0 (0)	0 (0)	2 (0.8)
End stage	0 (0)	6 (3.7)	1 (5.9)	4 (6.0)	11 (4.2)
C3, mean (SD), g/L	1.52 (0.261)	1.23 (0.211)	0 (0)	1.02 (0.200)	1.20 (0.241)

GA = geographic atrophy; nAMD = neovascular age-related macular degeneration; SD = standard deviation.

supporting KA to be the most influential parameter on pegcetacoplan exposure via intravitreal administration. A half-life of approximately 2 weeks based on the slowest rate process is supportive of a dosing frequency of monthly (approximately 2 half-lives) or every other month (approximately 4 half-lives) given the high maximal concentrations predicted in vitreous humor (Table 3) after direct intravitreal administration.

Systemic serum pegcetacoplan concentrations at steady state were predicted to be below the thresholds anticipated to result in meaningful inhibition of systemic C3 activation at clinically relevant doses (alternative pathway: half-

Table 2. Final Model-Predicted PK Parameter Estimates

PK Parameter	Estimate	Transformed Estimate*	Transformed 95% CI
CL/F, L/day	−1.12	0.325	0.307, 0.343
VC/F, L	0.603	1.83	1.62, 2.06
KA, day^{-1}	−2.94	0.0528	0.0493, 0.0567
Lambda (λ)	2.57	—	—
Age on CL/F (ϑ_6)	−0.559	—	—
C3 on CL/F (ϑ_7)	−0.350	—	—
Female sex on CL/F (ϑ_8)	−0.286	0.751	0.705, 0.800
Residual variability, %			
Log additive	0.300	30.0	28.7, 31.2
Interindividual variability, ω^2			
CL/F	0.0587	—	—
KA	0.122	36.0% CV	28.6% CV, 42.2% CV
Condition number	18		

CI = confidence interval; CL/F = apparent systemic clearance from serum; CV = coefficient of variation; KA = vitreous-to-serum absorption rate constant; PK = pharmacokinetic; VC/F = apparent volume of the central serum compartment.

η-shrinkage: 17.6% ($\eta_i^{CL/F}$), 17.6% (η_i^{KA}).
The following equations describe the covariate-parameter relationships in the model:

$$COVCL = \vartheta_6 \cdot (Log(Age) - Log(80\ years)) + \vartheta_7 \cdot (Log(Baseline\ C3) - Log(1.2\ g/L)) + \vartheta_8 \cdot FemaleSex$$

$$TETACL = \frac{(\exp(\eta_i^{CL/F} \cdot \lambda) - 1)}{\lambda}$$

$$CL/F_i = \exp(CL/F + COVCL + TETACL)$$

$$VC/F_i = \exp(VC/F)$$

$$KA_i = \exp(KA + \eta_i^{KA})$$

*For categorical covariates, transformed estimates represent the multiplicative difference in the parameter value from the reference category.

Table 3. Model-Predicted First Dose and Steady-State Exposure Metrics in Serum and Vitreous Humor

Pegcetacoplan Dose Regimen	Summary Statistic	First Dose					Steady-State					AR
		C_{max}, μg/mL	C_{min}, μg/mL	C_{avg}, μg/mL	AUC_{τ}, μg/mL· day	T_{max}, Days	C_{max}, μg/mL	C_{min}, μg/mL	C_{avg}, μg/mL	AUC_{τ}, μg/mL· day	T_{max}, Days	
Serum exposure												
15 mg monthly	Median	1.60	0.200	1.20	35.9	10.5	2.20	1.10	1.80	52.8	8.50	1.50
	5th, 9th percentile	0.900, 2.10	0.100, 0.300	0.700, 1.70	21.4, 49.6	7.50, 13.5	1.40, 3.00	0.500, 1.70	1.10, 2.50	32.4, 74.4	6.50, 9.50	1.20, 1.80
	Geometric mean	1.50	0.200	1.10	34.3	10.4	2.20	1.00	1.70	50.8	8.20	1.50
	Geometric % CV	29.1	26.2	30.1	30.1	20.9	25.9	43.9	30.6	30.6	14.2	14.5
15 mg every other month	Median	1.50	0.100	0.800	48.5	10.2	1.70	0.200	0.900	52.6	10.0	1.10
	5th, 9th percentile	0.600, 2.10	0.100, 0.200	0.300, 1.10	16.5, 65.3	6.00, 14.0	0.700, 2.20	0.100, 0.400	0.300, 1.20	17.9, 71.1	5.70, 12.5	1.00, 1.30
	Geometric mean	1.40	0.100	0.700	42.2	9.80	1.50	0.200	0.800	46.2	9.40	1.10
	Geometric % CV	53.4	47.1	50.9	50.9	26.2	46.1	70.5	46.0	46.0	24.7	8.35
Vitreous exposure												
15 mg monthly	Median	4523	794	1917	57 495	_	4724	974	2375	71 245	_	1.20
	5th, 9th percentile	4129, 5037	394, 1310	1503, 2335	45 077, 70 035	_	4172, 5710	422, 1960	1637, 3507	49 106, 105 210	_	1.10, 1.50
	Geometric mean	4550	771	1908	57 228	_	4815	964	2409	72 266	_	1.30
	Geometric % CV	6.68	42.2	14.7	14.7	_	12.1	55.8	26.7	26.7	_	12.3
15 mg every other month	Median	3903	157	1139	68 353	_	3909	159	1171	70 275	_	1.00
	5th, 9th percentile	3792, 4452	43.2, 712	840, 1835	50 379, 110 103	_	3792, 4614	42.1, 864	833, 2239	49 997, 134 325	_	1.00, 1.20
	Geometric mean	3974	158	1166	69 985	_	4008	164	1229	73 758	_	1.10
	Geometric % CV	5.81	110	25.2	25.2	_	7.88	124	33.1	33.1	_	8.15

AR = accumulation ratio; AUCτ = area under the concentration-time curve for dosing interval τ; C_{avg} = average concentration; C_{max} = maximum concentration; C_{min} = minimum concentration; CV = coefficient of variation; T_{max} = time to maximum serum concentration.
N = 121 patients with geographic atrophy receiving pegcetacoplan 15 mg monthly and 110 patients with geographic atrophy receiving pegcetacoplan 15 mg every other month.

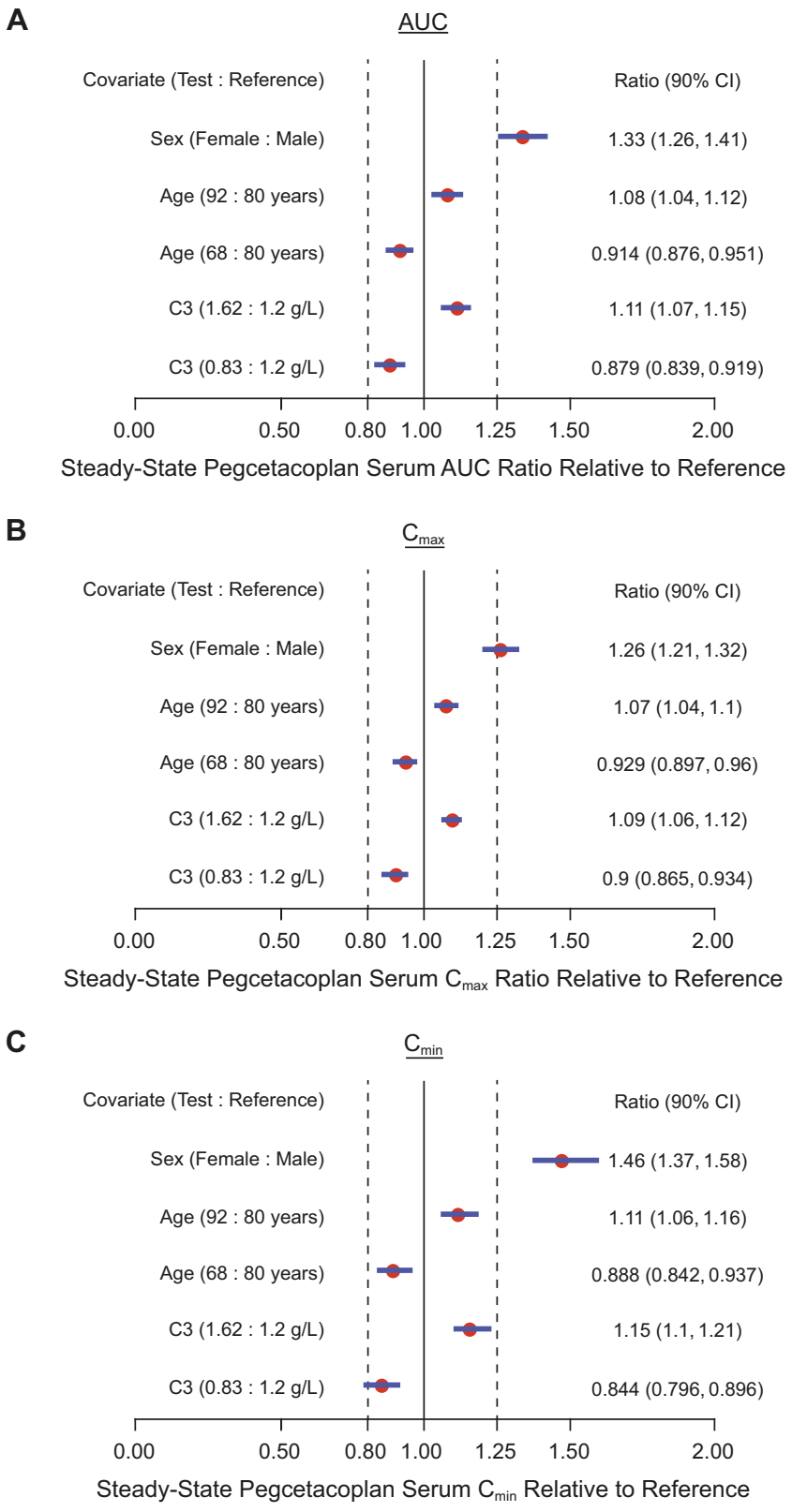

Figure 2. Patient and clinical characteristic covariate analyses: steady-state pegcetacoplan (**A**) AUC ratio, (**B**) serum C_{max} ratio, and (**C**) serum C_{min} ratio relative to reference. AUC = area under the concentration-time curve; CI = confidence interval; C_{max} = maximum concentration; C_{min} = minimum concentration.

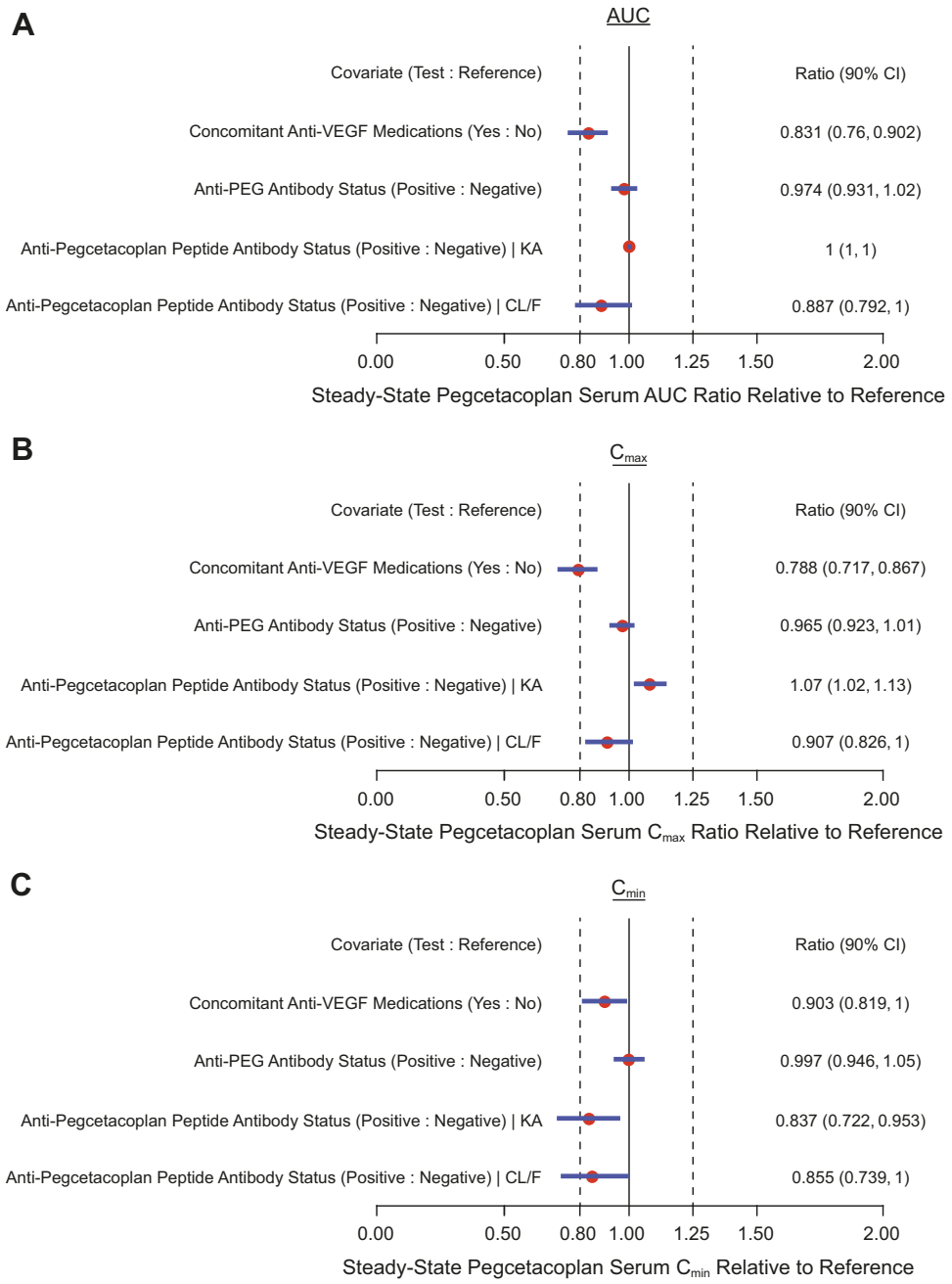

Figure 3. Influence of concomitant anti-VEGF administration and antidrug antibodies on steady-state pegcetacoplan (**A**) AUC ratio, (**B**) serum C_{max} ratio, and (**C**) serum C_{min} ratio relative to reference. AUC = area under the concentration-time curve; CI = confidence interval; CL/F = apparent systemic clearance from serum; C_{max} = maximum concentration; C_{min} = minimum concentration; KA = vitreous-to-serum absorption rate constant; PEG = polyethylene glycol.

maximal effective concentration [EC_{50}] 2.77 µg/mL; classical pathway: EC_{50} 5.90 µg/mL).[17] The systemic serum pegcetacoplan concentration required to achieve 1% of the maximum lactate dehydrogenase response in patients with paroxysmal nocturnal hemoglobinuria was 49 µg/mL (unpublished data). Exposure of pegcetacoplan in the vitreous humor was predicted to be >1300-fold higher than exposure in serum by ratio of steady-state AUC. There was minimal to no predicted accumulation of pegcetacoplan in the vitreous humor with monthly or every-other-month dosing considering the mean accumulation ratios of 1.30 and 1.10, respectively; consequently, no delay in onset of concentration-dependent effects was predicted due to accumulation at the target site. In comparison, VEGF inhibitors bevacizumab and aflibercept showed systemic serum accumulation and suppression of free serum VEGF for approximately 1 week after intravitreal injection.[18] The results of a PK/pharmacodynamic analysis performed to determine the

effect of individual predicted vitreous humor pegcetacoplan concentration on the rate of GA lesion progression are reported in a separate publication.[19] Although the continuous covariates of age and baseline C3 had no impact, female sex was predicted to result in a 1.26-fold increase in steady-state serum C_{max}. Based on prior knowledge on the impact of body weight on serum pegcetacoplan clearance following subcutaneous or intravenous administration, it is likely that some of the effect predicted for sex was a result of differences in body weight by sex. Nevertheless, the increase in serum exposure for females relative to males did not appear to be clinically meaningful considering the low absolute serum pegcetacoplan concentrations predicted (<5 μg/mL) and lack of predicted impact on vitreous exposure. Time-varying covariates, including concomitant anti-VEGF medication, were also assessed in post hoc covariate models. Concomitant treatment with anti-VEGF medications was not predicted to affect pegcetacoplan exposure in vitreous humor due to the estimate of the multiplicative effect of concomitant anti-VEGF use on KA including the null value of 1.

The data presented here are based on PK parameters predicted using a compartmental model rather than non-compartmental analysis of observed clinical trial data. However, our model is robust based on several criteria including precise estimation of all parameters (relative standard error <30%), stable condition number (18), and low η-shrinkage (<20%), and demonstrated adequate predictive ability for the observed serum concentration-time data and fraction of BLQ concentrations in visual predictive checks. A similar modeling approach and model structure was effectively used previously by Xu et al to draw inference regarding vitreous exposure of ranibizumab after intravitreal administration.[10] A comparable model was also effectively utilized in a study using data from patients treated for diabetic macular edema to assess the impact of renal function on PK of pegaptanib.[11]

The population PK model including first-order absorption from the vitreous to serum compartments, 1-compartment systemic disposition, and first-order elimination from the serum compartment adequately described the serum concentration-time profile of pegcetacoplan after intravitreal administration to adults with GA or nAMD. Pegcetacoplan disposition was absorption limited and steady-state serum pegcetacoplan exposure was predicted to be below the level required for systemic pharmacodynamic effects. The results of covariate analyses indicate that intrinsic and extrinsic factors are not predicted to have a clinically meaningful effect on vitreous exposure of pegcetacoplan.

Footnotes and Disclosures

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R.R.: Former employee and shares − Apellis Pharmaceuticals.

S.C.: President and CEO − A2-Ai LLC; Consultant - Apellis Pharmaceuticals.

R.L.C.: Former employee and shares − Apellis Pharmaceuticals; Current employee − A2-Ai LLC; Consultant - Apellis Pharmaceuticals.

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HUMAN SUBJECTS: Human subjects were included in this study. The clinical trials included in this study (NCT03525600, NCT02503332, NCT02461771, and NCT03465709) were conducted in accordance with the principles of the Declaration of Helsinki, and all participants provided written informed consent prior to enrollment. The protocols and informed consent forms were approved by the institutional review board for each study center.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Crass, Prem, Gauderault, Smith, Epling

Data collection: Crass, Prem, Gauderault, Smith, Epling

Analysis and interpretation: Crass, Prem, Gauderault, Ribeiro, Baumal, Smith, Epling, Chapel

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **AUC** = area under the curve; **BLQ** = below the limit of quantification; **CI** = confidence interval; **CL** = clearance; **CL/F** = apparent systemic clearance from serum; **C_{max}** = maximum concentration; **GA** = geographic atrophy; **KA** = vitreous-to-serum absorption rate constant; **nAMD** = neovascular age-related macular degeneration; **PK** = pharmacokinetics; **VC** = volume of central compartment; **VC/F** = apparent volume of the central serum compartment.

Keywords:
age-related macular degeneration, geographic atrophy, pharmacokinetics, pegcetacoplan, systemic absorption.

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