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RESEARCH**

APPLICATION NUMBER:

761355Orig1s000

CLINICAL PHARMACOLOGY
REVIEW(S)

Office of Clinical Pharmacology Review

BLA Number	761355
Link to EDR	\\CDSESUB1\evsprod\BLA761355\0001
Submission Date	12/27/2022
Submission Type	BLA; Priority review
Brand Name	EYLEA HD
Generic Name	Aflibercept
Dosage Form	Injection: 8 mg/0.07 mL solution in a single-dose vial
Route of Administration	Intravitreal injection
Proposed Indication	For the treatment of patients with: • Neovascular (Wet) Age-Related Macular Degeneration (nAMD) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR)
Proposed Dosing Regimen	(b) (4)
Applicant	Regeneron Pharmaceuticals, Inc.
Associated IND	IND 12462
OCP Review Team	Lei He, Ph.D.; Hezhen Wang, Ph.D.; Youwei Bi, Ph.D.; Ping Ji, Ph.D.
OCP Final Signatory	Suresh Doddapaneni, Ph.D., Director (Acting), Division of Immune and Inflammation Pharmacology, Office of Clinical Pharmacology

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1 EXECUTIVE SUMMARY

EYLEA (aflibercept) is a vascular endothelial growth factor (VEGF) inhibitor and has been approved for the treatment of patients with neovascular (Wet) Age-Related Macular Degeneration (nAMD), macular Edema Following Retinal Vein Occlusion (RVO), diabetic Macular Edema (DME), and diabetic Retinopathy (DR) under BLA 125387 (by Regeneron Pharmaceuticals, Inc.). The approved dosage forms are 2 mg/0.05 mL solution in a single-dose pre-filled syringe or in a single-dose vial for intravitreal (IVT) injection. The approved dosing regimens are:

- nAMD: 2 mg (0.05 mL) administered by IVT injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via IVT injection once every 8 weeks (2 months). Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months). Patients may also be treated with one dose every 12 weeks after one year of effective therapy.
- DME and DR: 2 mg (0.05 mL) administered by IVT injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via IVT injection once every 8 weeks (2 months). Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

On December 27, 2022, Regeneron submitted BLA 761355 seeking the marketing approval for 8 mg aflibercept ophthalmic solution (HD aflibercept) for the treatment of nAMD, DME, and DR. The proposed dosage form is 8 mg/0.07 mL solution in a single-dose vial for IVT injection. (b) (4)

(b) (4)

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(b) (4)

BLA761355 consists of one phase 2 study in nAMD (CANDELA), one phase2/3 study in DME (PHOTON), and one phase 3 study nAMD (PULSAR). In addition, two population PK reports and one exposure-response analysis report were submitted.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Immune and Inflammation Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology data submitted in support of BLA 761355 and finds the application acceptable from a clinical pharmacology perspective. The key review issues and recommendations are shown in Table 1.

Table 1. Review issues, recommendations, and comments of BLA 761355

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Three clinical studies in patients with nAMD and DME provide primary evidence of effectiveness (refer to the clinical review and statistical review for detailed assessment).
General dosing instructions	(b) (4) is acceptable from a clinical pharmacology perspective.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustment is needed for patients based on intrinsic and extrinsic factors.
Labeling	The proposed labeling concepts are generally acceptable.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the phase 2 and phase 3 studies.

1.2 Post Marketing Requirement

None.

2 SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kDa and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

HD aflibercept (8 mg aflibercept ophthalmic solution) is proposed to be administered intravitreally to exert local effects in the eye. In patients with nAMD or DME, following IVT administration of HD aflibercept, a fraction of the administered dose is expected to bind with endogenous VEGF in the eye to form an inactive aflibercept: VEGF complex. Once absorbed into the systemic circulation, aflibercept presents in the plasma as free aflibercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (i.e.,

aflibercept: VEGF complex, or bound aflibercept). The clinical pharmacokinetics of HD aflibercept is summarized as below:

- In patients with nAMD (Studies CANDELA and PULSAR), following IVT administration of HD aflibercept, the mean C_{max} and median T_{max} of free aflibercept in plasma ranged 0.14-0.29 mg/L and 1.05-1.93 days, respectively (Table 12, Table 21).
- In patients with DME (Study PHOTON), following IVT administration of HD aflibercept, the mean C_{max} and median T_{max} of free aflibercept in plasma was 0.31 mg/L and 0.96 days, respectively (Table 16).
- Population PK analysis showed that HD aflibercept PK is comparable between patients with nAMD and DME. Simulations indicated that following unilateral IVT administration of HD aflibercept, the mean C_{max} and median T_{max} of free aflibercept in plasma was estimated to be 0.30 mg/L and 2.9 days, respectively, in the combined nAMD and DME population.
- Population PK analysis showed that the systemic exposures of aflibercept (free and adjusted bound aflibercept) in patients with mild to severe renal impairment or mild hepatic impairment are comparable to those with normal organ function. No data for patients with moderate and severe hepatic impairment are available.
- Based on population PK covariates analysis, no dose adjustment is recommended by body weight, age, albumin, disease population, and race.
- Following IVT administration of HD aflibercept, the PD effect (decrease in central retinal thickness (CRT)) is comparable with 2 mg aflibercept in patients with nAMD or DME (Studies CANDELA, PULSAR, and PHOTON) (Figure 1, Figure 2, Figure 3)
- The incidence of treatment-emergent anti-drug antibody (ADA) to both 2 mg aflibercept (1.0%) and HD aflibercept (2.7%) are generally low and within the same range of that with EYLEA (1-3%) (Table 6). All samples from subjects with positive ADA were tested negative for neutralizing antibody (NAb). No relevant impact of treatment-emergent ADAs on the safety profile was observed.

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

(b) (4)

2.2.2 Therapeutic Individualization

Therapeutic individualization is not needed for the proposed HD aflibercept.

2.2.3 Outstanding Issues

None.

2.2.4 Summary of Labeling Recommendations

The proposed labeling concepts are generally acceptable.

3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Aflibercept is a VEGF inhibitor. EYLEA (aflibercept) injection (2 mg/0.05 mL solution for IVT use) has been approved for the treatment of patients with nAMD, RVO, DME, and DR under BLA 125387 (by Regeneron). Refer to the approved labeling of EYLEA for more detailed information.

In the Type B pre-IND meeting dated January 22, 2019, the Agency did not agree (b) (4)



In the Type B pre-BLA meeting dated September 26, 2022, the Agency clarified that it is acceptable to submit the application for the 8 mg product as a new BLA or as an efficacy supplement to the existing BLA for EYLEA. The clinical pharmacology team agreed that the proposed content and clinical pharmacology data package appeared reasonable pending review.

On December 27, 2022, Regeneron submitted BLA 761355 seeking the marketing approval for HD aflibercept (8 mg aflibercept ophthalmic solution) for the treatment of nAMD, DME, and DR.

3.2 General Pharmacology and Pharmacokinetic Characteristics

The clinical pharmacology of HD aflibercept were evaluated in three clinical studies in patients with nAMD and DME (Table 2).

General pharmacology and pharmacokinetic characteristics of HD aflibercept is summarized in Table 3. Aflibercept has been administered intravenously with doses up to 4 mg/kg in healthy subjects. Therefore, while the C_{max} of free aflibercept and adjusted bound aflibercept with HD aflibercept is up to 10-fold and 4-fold, respectively, higher than that with 2 mg aflibercept, the systemic exposure of HD aflibercept does not raise any safety concern (Table 4).

Table 2. Summary of clinical studies contributing to HD aflibercept pharmacokinetic, pharmacodynamic, and immunogenicity assessment

Study Number/ Report Location/ Study Status	Study Population	PK- and ADA-Related Objectives	Study Design and Duration	Treatment: Route of Administration, Frequency and Dose (number of participants analyzed for PK/ADA)
Neovascular age-related macular degeneration				
VGFTe (HD)- AMD-1905 (CANDELA) Phase 2 Module 5.3.5.1 End of the study date: 30 Nov 2021 Study completed	Men or women ≥ 50 years of age with active subfoveal CNV secondary to nAMD	- To assess the concentrations of free, bound, and total aflibercept in plasma over time. - To conduct exploratory PK/PD and/or dose/PD analyses on selected systemic and ocular response variables. Section 2.2.1 for results.	A phase 2, randomized, single-masked, repeat-dose study to evaluate the efficacy, safety, and tolerability of HD versus 2 mg aflibercept IVT in participants with nAMD. Duration: 44 weeks. Blood sample collection: Dense: Day 1 (predose, 4- and 8- hours post dose), 2, 3, 5, 8, 15, 22, 29, 57, 61, 85, 113, 141, 169, 225, and 309 (end of study) or early termination. Sparse: Day 1 (predose) and Weeks 8, approx. 9, 12, 24, 32, and 44 (end of study). ADA samples not collected in this study.	HD Aflibercept IVT, multiple dose: - HD (n = 53): 8 mg aflibercept monthly for 3 initial injections (baseline, week 4, and week 8), followed by additional doses at weeks 20 and 32. - Dense PK Samples: HD monthly (n = 15) Aflibercept 2 mg IVT, multiple dose: 2 mg (n = 52): aflibercept 2 mg monthly for 3 initial injections (baseline, week 4, and week 8), followed by additional doses at weeks 20 and 32. - Dense PK Samples: 2q8 (n = 15) Fellow eye administration: participants enrolled in the dense PK substudy were not allowed to receive treatment in the fellow eye (2 mg) before Week 12. Additional (rescue) treatment was permitted at Week 16 based on investigator judgment after consultation with the Sponsor. Participants were evaluated at weeks 24, 28, 36, and 40, and given a dose (at their randomized dose level, if either of the following criteria were met: - Loss of ≥ 5 letters from week 20 BCVA due to disease progression, or
20968 (PULSAR) Phase 3 Module 5.3.5.1 Data cutoff dates Efficacy/Safety 24 Aug 2022 PK and ADA 26 Aug 2022 (PK concentrations) 29 Aug 2022 (ADA) 09 Sep 2022 (PK parameters) Week 48 completed	Men or women ≥ 50 years of age with active subfoveal CNV secondary to nAMD	- To assess the concentrations of free, adjusted bound and total aflibercept in plasma over time. - To assess the immunogenicity of aflibercept. Section 2.2.2 for results.	A phase 3, randomized, double-masked, active-controlled study to investigate the efficacy, safety, and tolerability of IVT administration of HD aflibercept versus aflibercept 2 mg in participants with treatment-naïve nAMD Treatment duration: 92 weeks. Follow-up duration: 4 weeks. Blood sample collection: Dense: Day 1 (pre-dose, 4 and 8 hours post-dose) and on Days 2, 3, 5, 8, 15, and 22. Sparse: Day 1 (pre-dose), Week 4, Days 60-64, and Weeks 12, and 28. ADA sample collection: Baseline and Weeks 48 and 96.	- Anatomical findings that are considered vision-threatening. HD aflibercept 8 mg IVT, multiple dose: - HDq12 (n = 313): HD aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4week intervals. - HDq16 (n = 313): HD aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4week intervals. - Dense PK Samples: HDq12 + HDq16 (n = 16) Aflibercept 2 mg IVT, multiple dose: 2q8 (n = 308): aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4week intervals. - Dense PK Samples: 2q8 (n = 7) Fellow eye administration: participants enrolled in the dense PK substudy were not allowed to require treatment on the fellow eye (2 mg) at screening. DRM criteria for interval shortening are specified in Module 5.3.5.1 PULSAR W48 CSR Appendix 16.1.1 Section 7.1.
Diabetic macular edema				
VGFTe-HD- DME-1934 (PHOTON) Phase 2/3 Module 5.3.5.1	Men or women ≥ 18 years of age with type 1 or type 2 diabetes mellitus and DME. Participants with DME involving the center of the macula	To assess the concentrations of free, adjusted bound, and total aflibercept in plasma over time.	A phase 3, randomized, double-masked study in participants with DME involving the center of the macula to investigate the efficacy and safety of HD aflibercept versus 2 mg aflibercept.	HD aflibercept 8 mg IVT, multiple dose: HDq12 (n = 283): HD aflibercept 8 mg administered q12w, after 3 initial injections at q4w intervals (monthly)

Data cutoff dates Efficacy/Safety 19 Aug 2022		To assess the immunogenicity of aflibercept. Section 2.3.1 for results.	Duration: 96 weeks. Blood sample collection: Dense: Day 1 (pre-dose, 4 and 8 hours post-dose) and on Days 2, 3, 5, 8, 15, and 22. Sparse: Day 1 (predose), Weeks 4, 9, 12, 28, and 48. ADA sample collection: Baseline and Weeks 48 and 96.	- HDq16 (n = 135) HD aflibercept 8 mg administered q16w, after 3 initial injections at q4w intervals (monthly) - Dense PK Samples: HDq12 + HDq16 (n = 23) Aflibercept 2 mg IVT, multiple dose: - Every 8 weeks following 5 initial q4w (monthly) doses (n = 150). - Dense PK Samples: 2q8 (n = 12) Fellow eye administration: participants enrolled in the dense PK substudy were not allowed to receive 2 mg aflibercept in the fellow eye before providing a blood sample at Week 4. DRM criteria for interval shortening are specified in Module 5.3.5.1 PHOTON W48 CSR Appendix 16.1.1 Section 3.1.
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2q8 = 2 mg aflibercept every 8 weeks, ADA = anti-drug antibody, AMD = age-related macular degeneration, BCVA = best corrected visual acuity, CNV = choroidal neovascularization, DME = diabetic macular edema, DPKS = dense pharmacokinetic analysis set, DRM = dose regimen modification, HD = 8 mg aflibercept, HDq12 = aflibercept 8 mg administered every 12 weeks following 3 initial monthly injections, HDq16 = aflibercept 8 mg administered every 16 weeks following 3 initial monthly injections, IVT = intravitreal, n = number of participants assessed for PK/ADA, nAMD = neovascular age-related macular degeneration, PK = pharmacokinetic(s)
 Sources: Module 5.3.5.1 CANDELA CSR, Module 5.3.5.1 PULSAR W48 CSR, Module 5.3.5.1 PHOTON W48 CSR

Source: Table 2 of Summary of Clinical Pharmacology Studies

Table 3. Summary of Clinical Pharmacology and Pharmacokinetics

Information	Summary																																										
Bioanalysis	Free and bound aflibercept concentrations in human plasma were measured using validated enzyme-linked immunosorbent assays (ELISAs).																																										
Pharmacokinetics	Following IVT administration of HD aflibercept, a fraction of the administered dose is expected to bind with endogenous VEGF in the eye to form an inactive aflibercept: VEGF complex. Once absorbed into the systemic circulation, aflibercept presents in the plasma as free aflibercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (i.e., aflibercept: VEGF complex, or bound aflibercept). The PK parameters of free aflibercept following IVT administration are summarized as below: <table><tr><th>Study</th><th colspan="2">CANDELA</th><th colspan="2">PULSAR</th><th colspan="2">PHOTON</th></tr><tr><th>Study population</th><th colspan="2">nAMD</th><th colspan="2">nAMD</th><th colspan="2">DME</th></tr><tr><td>Dosage administration</td><td>IVT 2 mg (n=15)</td><td>IVT 8 mg (n=15)</td><td>IVT 2 mg (n=6)</td><td>IVT 8 mg (n=11)</td><td>IVT 2 mg (n=12)</td><td>IVT 8 mg (n=23)</td></tr><tr><td>Mean Cmax (SD) (mg/L)</td><td>0.03 (0.02)</td><td>0.29 (0.27)</td><td>0.08 (0.10)</td><td>0.14 (0.08)</td><td>0.03 (0.03)</td><td>0.31 (0.26)</td></tr><tr><td>Median (range) Tmax (days)</td><td>1.92 (0-4.01)</td><td>1.05 (0.15-4.02)</td><td>1.05 (0.33-1.95)</td><td>1.93 (0.33-4.03)</td><td>0.27 (0-7.04)</td><td>0.96 (0-4.01)</td></tr><tr><td>Mean elimination T1/2 (days)</td><td>9.77*</td><td>8.44</td><td>5.94</td><td>13.3</td><td>17.3*</td><td>8.43</td></tr></table> * Due to unquantifiable samples or infrequent sampling, data is limited (n=1 or 2) to characterize the terminal phase for free aflibercept in plasma. Population PK analysis showed that HD aflibercept PK (free and adjusted bound aflibercept) is comparable between patients with nAMD and DME. Simulations showed that following unilateral IVT administration of HD aflibercept, the mean (SD) Cmax and median Tmax of free aflibercept in plasma was estimated to be 0.30 (0.27) mg/L and 2.9 days, respectively, in	Study	CANDELA		PULSAR		PHOTON		Study population	nAMD		nAMD		DME		Dosage administration	IVT 2 mg (n=15)	IVT 8 mg (n=15)	IVT 2 mg (n=6)	IVT 8 mg (n=11)	IVT 2 mg (n=12)	IVT 8 mg (n=23)	Mean Cmax (SD) (mg/L)	0.03 (0.02)	0.29 (0.27)	0.08 (0.10)	0.14 (0.08)	0.03 (0.03)	0.31 (0.26)	Median (range) Tmax (days)	1.92 (0-4.01)	1.05 (0.15-4.02)	1.05 (0.33-1.95)	1.93 (0.33-4.03)	0.27 (0-7.04)	0.96 (0-4.01)	Mean elimination T1/2 (days)	9.77*	8.44	5.94	13.3	17.3*	8.43
Study	CANDELA		PULSAR		PHOTON																																						
Study population	nAMD		nAMD		DME																																						
Dosage administration	IVT 2 mg (n=15)	IVT 8 mg (n=15)	IVT 2 mg (n=6)	IVT 8 mg (n=11)	IVT 2 mg (n=12)	IVT 8 mg (n=23)																																					
Mean Cmax (SD) (mg/L)	0.03 (0.02)	0.29 (0.27)	0.08 (0.10)	0.14 (0.08)	0.03 (0.03)	0.31 (0.26)																																					
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Mean elimination T1/2 (days)	9.77*	8.44	5.94	13.3	17.3*	8.43																																					

	the combined nAMD and DME population. Following three initial monthly IVT doses of HD aflibercept, the mean accumulation ratio was predicted to be 1.2.	
Intrinsic factors	HD aflibercept (8 mg)	EYLEA (aflibercept) (2 mg)
	Based on population PK analysis: - The systemic exposures of aflibercept (free and adjusted bound aflibercept) in patients with mild to severe renal impairment (eGFR 15 to < 90 mL/min, estimated using CKD-EPI equation) are comparable to those with normal renal function. - The systemic exposures of aflibercept (free and adjusted bound aflibercept) in patients with mild hepatic impairment are comparable to patients with normal hepatic function. No data for patients with moderate and severe hepatic impairment are available. - No dose adjustment is needed based on the assessed covariates, including body weight, age, albumin, disease population, and race.	Per the labeling of EYLEA: - Pharmacokinetic analysis of a subgroup of patients (n=492) in one wet AMD study, of which 43% had renal impairment (mild n=120, moderate n=74, and severe n=16), revealed no differences with respect to plasma concentrations of free aflibercept after IVT administration every 4 or 8 weeks. Similar results were seen in patients in a RVO study and in patients in a DME study. No dose adjustment based on renal impairment status is needed for either wet AMD, RVO, or DME patients. - No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).
Pharmacodynamics	HD aflibercept (8 mg)	EYLEA (aflibercept) (2 mg)
	In Studies CANDELA, PULSAR, and PHOTON: Following IVT administration of HD aflibercept, the PD effect (decrease in CRT) is comparable with 2 mg aflibercept in patients with nAMD or DME (Figure 1, Figure 2, Figure 3).	Per the labeling of EYLEA: - nAMD: In the clinical studies anatomic measures of disease activity improved similarly in all treatment groups from baseline to week 52. Anatomic data were not used to influence treatment decisions during the first year. - DME: Reductions in mean retinal thickness were observed in VIVID and VISTA at weeks 52 and 100 compared to baseline. Anatomic data were not used to influence EYLEA treatment decisions
Immunogenicity	HD aflibercept (8 mg)	EYLEA (aflibercept) (2 mg)
	In Studies PULSAR (nAMD) and PHOTON (DME): During the 48-week treatment with aflibercept IVT injection, the incidence of treatment-emergent ADA was 1.0% (4/397) in 2 mg aflibercept group and 2.7% (25/937) in the combined HD aflibercept treatment group (Table 6). All samples from subjects with positive ADA were tested	Per the labeling of EYLEA: In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

	negative for NAb. No relevant impact of treatment-emergent ADAs on the safety profile was observed.	
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Table 4. Comparison of the mean Cmax (mg/L) (CV%) of free and adjusted bound aflibercept across clinical studies

Study	CANDELA		PULSAR		PHOTON		PDY6656*
Study population	nAMD		nAMD		DME		Healthy subjects
Dosage administration	IVT 2 mg (n=15)	IVT 8 mg (n=15)	IVT 2 mg (n=6)	IVT 8 mg (n=11)	IVT 2 mg (n=12)	IVT 8 mg (n=23)	IV 4 mg/kg (n=12)
Cmax of free aflibercept	0.03 (86)	0.29 (94)	0.08 (136)	0.14 (55)	0.03 (125)	0.31 (85)	78.6 (15)
Cmax of adjusted bound aflibercept**	0.18 (74)	0.46 (38)	0.18 (53)	0.44 (31)	0.12 (38)	0.39 (35)	2.72 (31)

The lower limit of quantification (LLOQ) for the free and bound assays is 15.6 ng/mL and 31.3 ng/mL, respectively.

*Data from Table 2 of BLA125387 Summary of Clinical Pharmacology.

** Adjusted bound aflibercept: the concentration of the bound aflibercept complex is adjusted by multiplying the bound aflibercept concentration by 0.717 to account for the difference in molecular weight and normalize the relative concentrations between free and bound aflibercept.

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 proposed HD aflibercept was developed to deliver a higher dose (8 mg) of aflibercept via IVT to extend the treatment interval as compared to 2 mg aflibercept. The clinical pharmacology data provide supportive evidence of effectiveness of HD aflibercept.

Based on population PK analysis, the median time for free aflibercept plasma concentrations to reach LLOQ following HDq12 or HDq16 dosing (3.5 weeks) was more than 2 folds as compared to the median time needed to reach LLOQ following aflibercept 2q8 (1.5 weeks) (Table 5). In ocular, HD aflibercept (8 mg dose) was estimated to have 34% lower clearance from the ocular compartment compared to the lower IVT aflibercept doses (≤ 4 mg). The median time for free aflibercept to reach the adjusted LLOQ in the ocular compartment increased from 8.7 weeks after a 2 mg IVT dose to 15 weeks after an 8 mg IVT dose, suggesting additional 6- week free aflibercept ocular exposure with HD aflibercept relative to 2 mg aflibercept. The popPK model well described the plasma concentration of aflibercept. Exploratory analyses suggest the slower ocular clearance and longer duration of free aflibercept ocular exposure of HD aflibercept contribute to the drug effect of HD aflibercept. But as there is no observed ocular concentration of aflibercept to confirm the prediction, such interpretation should be treated with caution.

The ocular PD effects of aflibercept were also evaluated by measurement of CRT in HD aflibercept clinical development program in patients with nAMD or DME (Studies CANDELA, PULSAR, and PHOTON). Results showed that following the IVT dose of 2 mg aflibercept and 8 mg HD aflibercept, similar PD effect (decrease in CRT) was observed 4 weeks after each initial q4w dose through 12 weeks, in either the nAMD or DME population (Figure 1, Figure 2, Figure 3).

Refer to the clinical rand statistical review for more detailed efficacy assessment.

Table 5. Summary of model-predicted time to LLOQ of free aflibercept in plasma following IVT for combined participants with nAMD and DME

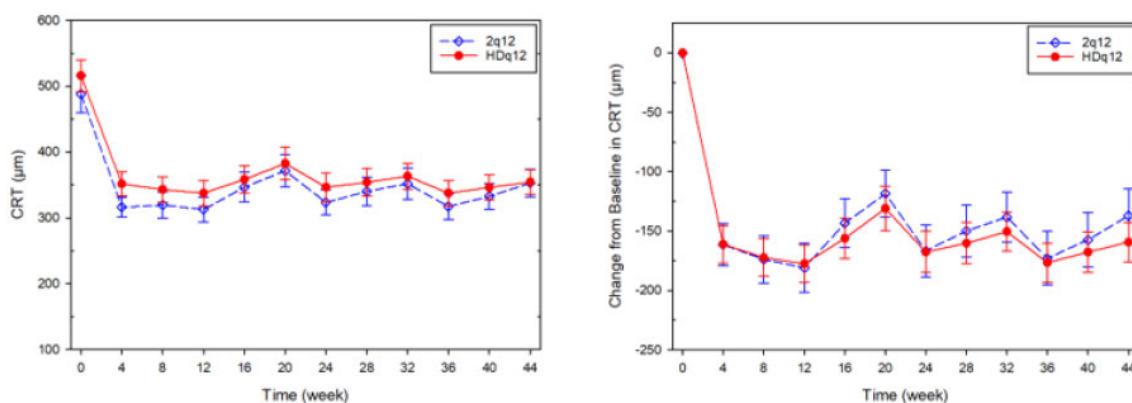
Regimen	Mean (SD) Week	Median (90% PI) Week
2q8	1.58 (0.712)	1.5 (0.524, 2.82)
HDq12	3.81 (1.61)	3.51 (1.83, 6.81)
HDq16	3.79 (1.58)	3.50 (1.83, 6.73)

Model-predicted time = time after a single IVT dose of the 2q8, HDq12 or HDq16 regimens.

2q8 = aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals, DME = diabetic macular edema, HDq12 = aflibercept 8 mg administered every 12 weeks following 3 initial monthly injections, HDq16 = aflibercept 8 mg administered every 16 weeks following 3 initial monthly injections, IVT = intravitreally, LLOQ = lower limit of quantification, nAMD = neovascular age related macular degeneration, PI = prediction interval, SD = standard deviation

Source: Module 5.3.3.5 Population PK Simulation Report Table 7

Figure 1. Mean (SE) change in absolute CRT (left panel) and change from baseline in CRT (right panel) over time following administration of 2q12 and HDq12 intravitreal doses of aflibercept in participants with nAMD (Study CANDELA)

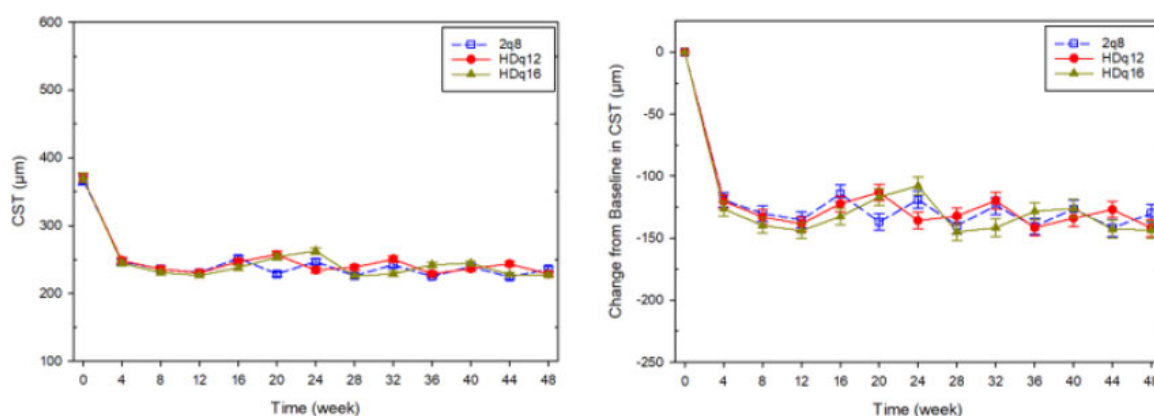


2q12 = 2 mg aflibercept every 12 weeks following 3 initial monthly doses, CRT = central retinal thickness, HDq12 = aflibercept 8 mg administered every 12 weeks following 3 initial monthly doses, LOCF = last observation carried forward, nAMD = neovascular age-related macular degeneration, SE = standard error

Note: results from the FAS are presented. The LOCF method was used for imputing missing values.

Source: Module 5.3.5.1 CANDELA CSR Table 14.02.08/5.a

Figure 2. Mean (SE) change in absolute CST (left panel) and change from baseline in CST (right panel) over time following administration of 2q8, HDq12, and HDq16 intravitreal doses of aflibercept in participants with nAMD (Study PULSAR)

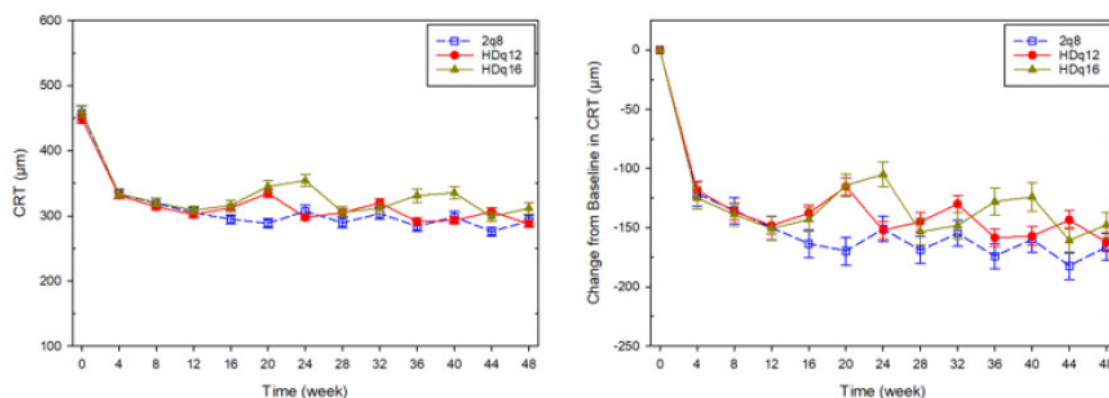


2q8 = 2 mg aflibercept every 8 weeks following 3 initial monthly doses, CST = central subfield thickness, HDq12 = aflibercept 8 mg administered every 12 weeks following 3 initial monthly doses, HDq16 = aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals, LOCF = last observation carried forward, nAMD = neovascular age-related macular degeneration

Note: results from the FAS are presented. The LOCF method was used for imputing missing values.

Source: Module 5.3.5.1 PULSAR W48 CSR, Table 14.2.3/22.

Figure 3. Mean (SE) change in absolute CRT (left panel) and change from baseline in CRT (right panel) over time following administration of 2q8, HDq12, and HDq16 intravitreal doses of aflibercept in participants with DME (Study PHOTON)



2q8 = 2 mg aflibercept every 8 weeks following 3 initial monthly doses, CRT = central retinal thickness, DME = diabetic macular edema, HDq12 = aflibercept 8 mg administered every 12 weeks following 3 initial monthly doses, HDq16 = aflibercept 8 mg administered every 16 weeks following 3 initial monthly doses, LOCF = last observation carried forward, SE = standard error

Note: results from the FAS are presented. The LOCF method was used for imputing missing values.

Source: Module 5.3.5.1 PHOTON W48 CSR, Table 14.2.3.4.4

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

The proposed dosing regimen is appropriate for the general patient population with nAMD, DME, or DR from a clinical pharmacology perspective.

The efficacy and safety of HD aflibercept (b) (4) has been evaluated in three phase 2 and phase 3 clinical studies in subjects with nAMD (CANDELA and PULSAR) and subjects with DME and DR (PHOTON). Refer to the clinical and statistical review for detailed benefit/risk assessment.

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

Population PK analysis did not identify any covariate with a clinically meaningful impact on the systemic exposure of free and adjusted bound aflibercept. Therefore, an alternate dosing regimen is not needed for subpopulations based on intrinsic factors.

3.3.4 What is the immunogenicity of the proposed drug product?

Immunogenicity was assessed in patients with nAMD or DME (Table 6). The pre-treatment incidence of ADA is 2.5% (10/397) in 2 mg aflibercept group and 2.5% (23/937) in HD aflibercept groups. During the 48-week treatment with aflibercept IVT injection, the incidence of treatment-emergent ADA was 1.0% (4/397) in 2 mg aflibercept group and 2.7% (25/937) in the combined HD aflibercept treatment group. All the treatment-emergent ADA were indeterminate and with the titer <1000. None of these ADA positive samples demonstrated neutralizing activity.

The safety profile of patients with treatment-emergent ADAs was reviewed for reactions potentially related to immunogenicity such as intraocular inflammations, hypersensitivity, rash, pruritus, and urticaria. For one participant with positive ADAs, a non-serious Iritis was reported (mild, resolved). No other immunogenicity reactions were reported in patients with positive ADAs.

Overall, the incidence of treatment-emergent ADA to both 2 mg aflibercept and HD aflibercept are generally low and within the same range with EYLEA (1% to 3%). No relevant impact of treatment-emergent ADAs on the safety profile was observed.

Table 6. Summary of immunogenicity assessment by treatment group in patients with nAMD or DME

ADA Status/Category Max. Titer Category NAb Status	Aflibercept		HD Aflibercept	
	2q8 n (%)	HDq12 n (%)	HDq16 n (%)	HDq12+HDq16 n (%)
ADA				
ADA Analysis Set	397 (100%)	532 (100%)	405 (100%)	937 (100%)
Negative	383 (96.5%)	501 (94.2%)	388 (95.8%)	889 (94.9%)
Pre-existing Immunoreactivity	10 (2.5%)	17 (3.2%)	6 (1.5%)	23 (2.5%)
Treatment-Boosted Response	0	0	0	0
Treatment-Emergent Response	4 (1.0%)	14 (2.6%)	11 (2.7%)	25 (2.7%)
Persistent	0	0	0	0
Indeterminate	4 (1.0%)	14 (2.6%)	11 (2.7%)	25 (2.7%)
Transient	0	0	0	0
TE & TB Maximum Titer Category				
Low (<1,000)	4 (1.0%)	14 (2.6%)	11 (2.7%)	25 (2.7%)
Moderate (1,000 to 10,000)	0	0	0	0
High (>10,000)	0	0	0	0
NAb				
NAb Analysis Set	393 (99.0%)	530 (99.6%)	404 (99.8%)	934 (99.7%)
NAb Negative	393 (99.0%)	530 (99.6%)	404 (99.8%)	934 (99.7%)
NAb Positive	0	0	0	0

2q8 = 2 mg aflibercept every 8 weeks, AAS = ADA analysis set, ADA = anti-drug antibody, DME = diabetic macular edema, HDq12 = high dose (8 mg) aflibercept every 12 weeks, HDq16 = high dose (8 mg) aflibercept every 16 weeks, n = number of participants, NAb = neutralizing antibodies, nAMD = neurovascular age-related macular degeneration, TB = treatment-boosted, TE = treatment-emergent

Note: Percentages are based on ADA analysis set. Data from WK 48 lock for PHOTON and PULSAR are included in the analysis. Data source: immunogenicity data from the week 48 database lock for PULSAR and PHOTON.

Source: Table 19 of Summary of Clinical Pharmacology Studies

4 APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Enzyme-linked immunosorbent assays (ELISAs) have been developed and validated to determine the concentrations of free and bound aflibercept in human plasma respectively in the original BLA submission. Refer to the clinical pharmacology review for BLA125387 for more details of the method validation. During the development program for HD aflibercept, assay modifications have been made on these two assays, including utilizing standards prepared in neat plasma, analyzing standards, quality controls (QCs), or samples in duplicate instead of triplicate to increase sample throughput, using a new regression model for data analysis. The new assays were validated for analysis of samples collected in CTAD (citrate, theophylline, adenosine, and dipyridamole) plasma as well as sodium citrate plasma and were also cross-validated against the original assays (Table 7, Table 8, Table 9, Table 10). All human plasma samples from Studies CANDELA, PULSA, and PHOTO) were analyzed within the 24-month long-term storage period established during the validation of the methods.

Table 7. Summary of the bioanalytical assay for the quantitative measurement of free aflibercept in human CTAD plasma (Validation Report VGFT-AV-16174-VA-01V1)

Assay Information, Validation Parameters And Acceptance Criteria	Results
Analyte	VEGF Trap
Capture Reagent	Human VEGF₁₆₅ (REGN110)
Detection Reagents	Mouse anti-VEGF Trap mAb (REGN19) + Goat Anti-Mouse IgG Fcγ - HRP
Assay Range Neat human plasma (ULOQ - LLOQ) 10% human plasma (Assay MRD = 1:10)	1000 – 15.6 ng/mL 100 - 1.56 ng/mL
Inter-assay Accuracy and Precision %AR CV% Dose Total Error ≤ 30% (ULOQ and LLOQ ≤ 40%)	87 – 98% 2 – 6% 4 – 19%
Sensitivity and Range %AR 80 - 120% (ULOQ and LLOQ 75 - 125%) CV% Dose ≤ 20% (ULOQ and LLOQ ≤ 25%)	87 – 98% 2 – 6%
Inter-assay Linearity %AR 80 - 120% (Standards 1 and 7: 75 - 125%) CV% Dose ≤ 20% (Standards 1 and 7: ≤ 25%)	99 – 103% 1 – 4%
Intra-assay Accuracy and Precision %AR CV% Dose Total Error ≤ 30% (LLOQ ≤ 40%)	82 – 102% 1 – 15% 1 – 24%
Intra-assay Linearity %AR 80 - 120% (Standards 1 and 7: 75 - 125%) CV% Dose ≤ 20% (Standards 1 and 7: ≤ 25%)	95 – 105% 1 – 3%
Matrix Interference At least 80% of the naïve individual samples must be < LLOQ	100% (10 of 10 samples BLQ)
Selectivity at LLOQ (15.6 ng/mL) %AR 75-125%, CV% Dose ≤ 25% for at least 80% of LLOQ-spiked naïve individual samples	89 - 98%, 0 – 5% (10 of 10 samples)
Dilution Recovery (High Level Quality Controls) %dAR 80 - 120% CV% Dose ≤ 20%	81 – 109% 1 – 5%
Robustness (Standards, Quality Controls) %AR 80 - 120% (Standards 1 and 7, ULOQ and LLOQ 75 - 125%) CV% Dose ≤ 20% (Standards 1 and 7, ULOQ and LLOQ ≤ 25%)	97 – 116% 0 – 4%
Ruggedness (Standards, Quality Controls) %AR 80 - 120% (Standards 1 and 7, ULOQ and LLOQ 75 - 125%) CV% Dose ≤ 20% (Standards 1 and 7, ULOQ and LLOQ ≤ 25%)	93 – 106% 0 – 18%
Specificity %AR 80 - 120%, CV% Dose ≤ 20% (Free VEGF Trap; 10X MQC) Free REGN110 must be BLQ	111%, 3% BLQ
Cross Validation with SOP-PCL113 Variability (%) ± 30%, CV% Dose ≤ 20% for at least 67% of individual samples	-22.26 – 20.04%, 0 – 6% (for 98% of the samples (47 of 48 samples))

Free aflibercept is stable in human CTAD plasma for at least 12 months at -20°C and 24 months at -80°C.

Source: page 7 of Validation Report VGFT-AV-16174-VA-01V1

Table 8. Summary of the bioanalytical assay for the quantitative measurement of free aflibercept in human sodium citrate plasma (Validation Report VGFT-AV-21020-VA-01V1)

Assay Information, Validation Parameters and Acceptance Criteria	Results
Analyte	VEGF Trap
Capture Reagent	Human VEGF₁₆₅ (REGN110)
Detection Reagents	Mouse anti-VEGF Trap mAb (REGN19) + Goat Anti-Mouse IgG Fcγ - HRP
Assay Range Neat human plasma (ULOQ - LLOQ) 10% human plasma (Assay MRD = 1:10)	1000 – 15.6 ng/mL 100 – 1.56 ng/mL
Linearity %AR 80 - 120% (Standards 1 and 7: 75 - 125%) CV% Conc ≤ 20% (Standards 1 and 7: ≤ 25%)	98 – 103% 1 – 2%
Inter-Assay Accuracy and Precision %AR CV% Conc Total Error ≤ 30% (ULOQ and LLOQ ≤ 40%)	93 – 113% 5 – 8% 8 – 20%
Intra-Assay Accuracy and Precision %AR CV% Conc Total Error ≤ 30% (ULOQ and LLOQ ≤ 40%)	86 – 122% 1 – 9% 2 – 24%
Matrix Interference At least 80% of the naïve individual samples must be < LLOQ	100% (10 of 10 samples BLQ)
Selectivity at LLOQ (15.6 ng/mL) and HQC (700 ng/mL) %AR 75 - 125%, CV% Conc ≤ 25% for at least 80% of the LLOQ-spiked naïve samples %AR 80 - 120%, CV% Conc ≤ 20% for at least 80% of the HQC-spiked naïve samples	82% – 89%, 0 – 4% (10 of 10 samples) 92% – 97%, 0 – 5% (10 of 10 samples)
Dilution Linearity (High Level Quality Control) %dAR 80 - 120% CV% Conc ≤ 20% Final CV% Conc ≤ 20%	90 – 115% 0 – 4% 1 – 2 %
Robustness (Standards, Quality Controls) %AR 80 - 120% (Standard 1, 7, ULOQ and LLOQ: 75 - 125%) CV% Conc ≤ 20% (Standard 1, 7, ULOQ and LLOQ: ≤ 25%)	87 – 109% 0 – 7%
Target Interference %AR 80 - 120%, CV% Conc ≤ 20% (HQC without VEGF ₁₆₅) %AR 80 - 120%, CV% Conc ≤ 20% (MQC without VEGF ₁₆₅) Free VEGF ₁₆₅ must be BLQ	107%, 2% 104%, 3% BLQ
Short-term Analyte Stability (4°C 24 hours, 6 hours Room Temperature, Freeze/Thaw - 8 Cycles) %AR 80 - 120%	102 – 116%

Bound aflibercept is stable in human CTAD plasma for at least 12 months at -20°C and 24 months at -80°C.
Source: page 7 of Validation Report VGFT-AV-21020-VA-01V1

Table 9. Summary of the bioanalytical assay for the quantitative measurement of bound aflibercept in human CTAD plasma (Validation Report VGFT-AV-17013-VA-01V1)

Assay Information, Validation Parameters And Acceptance Criteria	Results
Analyte	VEGF₁₆₅:VEGF Trap Complex (Bound VEGF Trap)
Capture Reagent	Goat anti-human VEGF₁₆₅ affinity purified antibody
Detection Reagents	Mouse anti-VEGF Trap mAb (REGN19) + Goat Anti-Mouse IgG Fcγ-HRP
Assay Range Neat human plasma (ULOQ - LLOQ) 10% human plasma (Assay MRD = 1:10)	2000 – 31.3 ng/mL 200 – 3.13 ng/mL
Inter-assay Accuracy and Precision %AR CV% Dose Total Error ≤ 30% (ULOQ and LLOQ ≤ 40%)	98 – 103% 3 – 6% 6 – 9%
Sensitivity and Range %AR 80 - 120% (ULOQ and LLOQ 75 - 125%) CV% Dose ≤ 20% (ULOQ and LLOQ ≤ 25%)	98 – 103% 3 – 6%
Inter-assay Linearity %AR 80 - 120% (Standards 1 and 7: 75 - 125%) CV% Dose ≤ 20% (Standards 1 and 7: ≤ 25%)	98 – 103% 1 – 2%
Intra-assay Accuracy and Precision %AR CV% Dose Total Error ≤ 30% (LLOQ ≤ 40%)	90 – 111% 1 – 10% 4 – 14%
Intra-assay Linearity %AR 80 - 120% (Standards 1 and 7: 75 - 125%) CV% Dose ≤ 20% (Standards 1 and 7: ≤ 25%)	95 – 107% 0 – 3%
Matrix Interference At least 80% of the naïve individual samples must be < LLOQ	100% (10 of 10 samples BLQ)
Selectivity at LLOQ (31.3 ng/mL) %AR 75-125%, CV% Dose ≤ 25% for at least 80% of LLOQ-spiked naïve individual samples	87 - 105%, 0 – 7% (10 of 10 samples)
Dilution Recovery (High Level Quality Controls) %dAR 80 - 120% CV% Dose ≤ 20%	107 – 117% 0 – 5%
Robustness (Standards, Quality Controls) %AR 80 - 120% (Standards 1 and 7, ULOQ and LLOQ 75 - 125%) CV% Dose ≤ 20% (Standards 1 and 7, ULOQ and LLOQ ≤ 25%)	94 – 112% 0 – 7%
Ruggedness (Standards, Quality Controls) %AR 80 - 120% (Standards 1 and 7, ULOQ and LLOQ 75 - 125%) CV% Dose ≤ 20% (Standards 1 and 7, ULOQ and LLOQ ≤ 25%)	94 – 108% 0 – 10%
Cross Validation with SOP PCL2088 Variability (%) ± 30%, CV% Dose ≤ 20% for at least 67% of individual samples	-6.92 – 12.61%, 0 – 5% (50 of 50 samples)

Free aflibercept is stable in human sodium citrate plasma for at least 24 months at -20°C or -80°C.

Source: page 7 of Validation Report VGFT-AV-17013-VA-01V1

Table 10. Summary of the bioanalytical assay for the quantitative measurement of bound aflibercept in human sodium citrate plasma (Validation Report VGFT-AV-21022-VA-01V1)

Assay Information, Validation Parameters and Acceptance Criteria	Results
Analyte	VEGF₁₆₅:VEGF Trap Complex (Bound VEGF Trap)
Capture Reagent	Goat anti-human VEGF₁₆₅ polyclonal antibody
Detection Antibody	Mouse anti-VEGF Trap mAb (REGN19) + Goat Anti-Mouse IgG Fcγ - HRP
Assay Range Neat human plasma (ULOQ - LLOQ) 10% human plasma (Assay MRD = 1:10)	2000 - 31.3 ng/mL 200 - 3.13 ng/mL
Linearity %AR 80 - 120% (Standards 1 and 7: 75 - 125%) CV% Conc ≤ 20% (Standards 1 and 7: ≤ 25%)	98-102% 0-2%
Inter-assay Accuracy and Precision %AR CV% Conc Total Error ≤ 30% (ULOQ and LLOQ ≤ 40%)	86-92% 5-6% 13-20%
Intra-assay Accuracy and Precision %AR CV% Conc Total Error ≤ 30% (ULOQ and LLOQ ≤ 40%)	79-99% 0-6% 6-24%
Matrix Interference At least 80% of the naïve individual samples must be < LLOQ	100% (10 of 10 samples BLQ)
Selectivity at LLOQ (31.3 ng/mL) and HQC (1500 ng/mL) %AR 75 - 125%, CV% Conc ≤ 25% for at least 80% of the LLOQ-spiked naïve individual samples %AR 80 - 120%, CV% Conc ≤ 20% for at least 80% of the HQC-spiked naïve individual samples	78-98%, 0-3% (10 of 10 samples) 89-103%, 0-4% (10 of 10 samples)
Dilution Linearity (High Level Quality Control) %dAR 80 - 120% CV% Conc ≤ 20% Final CV% ≤ 20%	92-103% 0-2% 2 - 5%
Robustness (Standards, Quality Controls) %AR 80 - 120% (Standards 1 and 7, ULOQ and LLOQ 75 - 125%) CV% Conc ≤ 20% (Standards 1 and 7, ULOQ and LLOQ: ≤ 25%)	89-105% 0-7%
Short-term Analyte Stability (4°C 24 hours, 6 hours Room Temperature, Freeze/Thaw - 8 Cycles) %AR 80 - 120%	83-93%

Bound aflibercept is stable in human sodium citrate plasma for at least 24 months at -20°C or -80°C.

Source: page 7 of Validation Report VGFT-AV-21022-VA-01V1

4.2 Clinical PK Assessment

Plasma concentrations of free and bound aflibercept in samples from clinical studies were measured using validated ELISA methods. The assay for bound aflibercept is calibrated using the VEGF:aflibercept standards, and the results are reported for bound aflibercept as weight per volume (eg, ng/mL or mg/L) of the VEGF:aflibercept complex. To account for the difference in molecular weight and normalize the relative concentrations between free and bound aflibercept, the concentration of the bound aflibercept complex is normalized to determine the amount of

aflibercept present in the bound aflibercept complex. The bound aflibercept complex consisted of 71.7% aflibercept and 28.3% human VEGF₁₆₅ based on the molecular weight of each component. Therefore, the concentration of the bound aflibercept complex was multiplied by 0.717 to yield the concentration of adjusted bound aflibercept (Equation 1). Total aflibercept was calculated by summing the plasma concentrations of free and adjusted bound aflibercept (Equation 2).

Equation 1:

Adjusted bound aflibercept (mg/L) = Bound aflibercept (mg/L) x 0.717

Equation 2:

Total aflibercept (mg/L) = Sum of adjusted bound aflibercept (mg/L) + free aflibercept (mg/L)

4.2.1 Phase 2 Study VGFTe (HD)-AMD-1905 (CANDELA)

Title: A Randomized, Single-Masked, Active-Controlled Phase 2 Study of the Safety, Tolerability, and Efficacy of Repeated Doses of High-Dose Aflibercept in Patients with Neovascular Age-Related Macular Degeneration

Study period: 04, Nov 2019- 30, Nov 2021

Objectives:

- Primary: safety, PD effect,
- Exploratory: efficacy, PK, PK/PD

Study design: This was a phase 2, multi-center, randomized, single-masked study in participants with nAMD that investigated the efficacy, safety, and tolerability of HD versus IAI. The study consisted of a screening/baseline period, a treatment period, and an end of study (EOS) visit at week 44.

Figure 4. Study design (Study CANDELA)

Multi-center, randomized, single-masked
Patients with neovascular AMD (treatment-naïve), N=100*
Randomized 1:1

IAI
3 initial monthly injections
n ≈ 50*

HD
3 initial monthly injections
n ≈ 50*

*Dense PK Substudy:
 ~15 patients per
 treatment group

Week 16:
Primary EP: % pts without fluid in the center subfield

Week 44 Analysis (End of Study)

Abbreviations: AMD=age-related macular degeneration; EP=endpoint; HD=high-dose aflibercept (8 mg) injection; IAI=intravitreal aflibercept (2 mg) injection; PK=pharmacokinetics; pts=participants.

Source: Figure 1 of Study CANDELA CSR

Test Drug Product

Study Drug Name	High-dose aflibercept	Intravitreal aflibercept injection
Type	Biologic	Biologic
Dose Formulation	Liquid formulation	Liquid formulation
Unit Dose Strength(s)	114.3 mg/mL	40 mg/mL
Dosage Level(s)	8 mg (70 µL)	2 mg (50 µL)
Route of Administration	IVT	IVT
Use	Experimental	Active-control
IMP	IMP	EYLEA
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Study drug was provided as liquid formulation in a vial. Each vial was labeled as required per country requirement	EYLEA was provided as liquid formulation in a vial. Each vial was labeled as required per country requirement
Alias(es)	HD	IAI (EYLEA)

Abbreviations: HD=high-dose aflibercept (8 mg) injection; IAI=intravitreal aflibercept (2 mg) injection; IMP=investigational medicinal product; IVT=intravitreal.

Source: Table 1 of Study CANDELA CSR

PK Sampling

Sparse PK sampling will be performed in all patients not enrolled in the dense PK sub-study: baseline, and on Days 57, 61, 85, 169, 225, 309 (EOS)

Dense PK sampling will be performed in approximately 30 patients (15 in each group) as shown in the table below.

Table 11. PK sampling schedule for dense PK sub-study (Study CANDELA)

Visit	Dose	Assessment Day and Time (h)		Dense PK Sample Collection	Heart Rate and Blood Pressure ^{1,2}	Urinalysis / UPCR
Visit 3 (Baseline)	X	1	Time of first dose	X (pre-dose)	X	
			4h post-dose (± 30 min) ³	X		
			8h post-dose (± 2 h) ⁴	X		
		2	± 2 h ⁵	X	X	
		3	± 2 h ⁵	X	X	
		5	± 2 h ⁵	X	X	
		8	± 2 h ⁵	X	X	X ⁶
		15	± 2 h ⁵	X	X	X ⁶
		22	± 2 h ⁵	X	X	

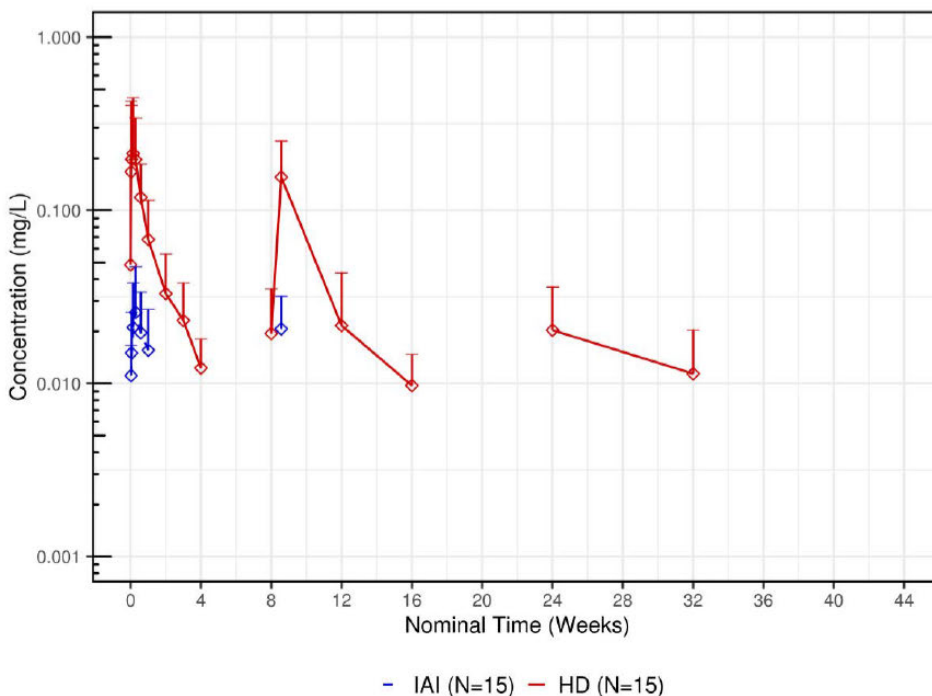
Source: Table 2 of Protocol VGFTe (HD)-AMD-1905 Amendment 3

PK Results

The PK profiles and PK parameters of free, adjusted, and total aflibercept in plasma are shown as below.

Free aflibercept in dense PK substudy

Figure 5. Mean (+SD) concentrations of free aflibercept in plasma by nominal time and treatment group in patients with nAMD (Study CANDELA, log-scaled, dense PK substudy)



N = Number of patients; SD = Standard deviation; IAI = Intravitreal aflibercept injection; HD = High-dose aflibercept injection
 Note: Concentrations below the lower limit of quantification (LLOQ) were set to LLOQ/2. Mean is set to missing if there are no or only 1 measurable concentration at a timepoint.
 /Data/Development/PK/VGFT/VGFT-HD-AMD/VGFTe-AMD-1905/Interim/Analysis_CSR/Programs/TFL/Figures/F_PCMNLOGSUBFR.sas (&_metauser 2022-07-15 14:01:01 SAS Linux 9.4).

Source: Figure 4 of Study CANDELA Clinical Pharmacology Report

Table 12. Summary of PK parameters of free aflibercept in plasma by treatment group in patients with nAMD (Study CANDELA, dense PK substudy)

PK Parameters	Unit	IAI (N=15)				HD (N=15)			
		n	Mean (SD)	Median	Min : Max	n	Mean (SD)	Median	Min : Max
AUC _{inf}	day*mg/L	0				12	2.01 (0.857)	2.12	0.520 : 3.15
AUC _{inf} /Dose	day*mg/L/mg	0				12	0.251 (0.107)	0.265	0.0649 : 0.394
AUC _{last}	day*mg/L	11	0.175 (0.198)	0.0924	0.00855 : 0.720	15	1.54 (0.874)	1.45	0.0424 : 2.98
AUC _{last} /Dose	day*mg/L/mg	11	0.0877 (0.0990)	0.0462	0.00428 : 0.360	15	0.193 (0.109)	0.181	0.00530 : 0.372
AUC ₀₋₂₈	day*mg/L	8	0.187 (0.257)	0.121	0 : 0.783	14	1.70 (0.782)	1.63	0.521 : 2.98
C _{max}	mg/L	15	0.0298 (0.0256)	0.0242	0 : 0.0861	15	0.286 (0.269)	0.220	0.0180 : 0.953
C _{max} /Dose	mg/L/mg	15	0.0149 (0.0128)	0.0121	0 : 0.0431	15	0.0358 (0.0336)	0.0275	0.00225 : 0.119
C _{last}	mg/L	11	0.0286 (0.0195)	0.0224	0.0171 : 0.0861	15	0.0233 (0.00783)	0.0194	0.0158 : 0.0425
C _{trough} (Week 12)/ C _{trough} (Week 4)		0				6	2.09 (1.51)	2.17	0 : 4.10
t _{1/2}	day	2	9.77 (---)	9.77	8.22 : 11.3	13	8.44 (4.95)	8.17	1.28 : 17.6
t _{max}	day	15	--	1.92	0 : 4.01	15	--	1.05	0.147 : 4.02
t _{last}	day	11	--	6.94	1.92 : 21.1	15	--	21.0	3.95 : 29.0

N = Number of patients; n = Number of patients contributing to each PK parameter; SD = Standard deviation; IAI = Intravitreal aflibercept injection; HD = High-dose aflibercept injection

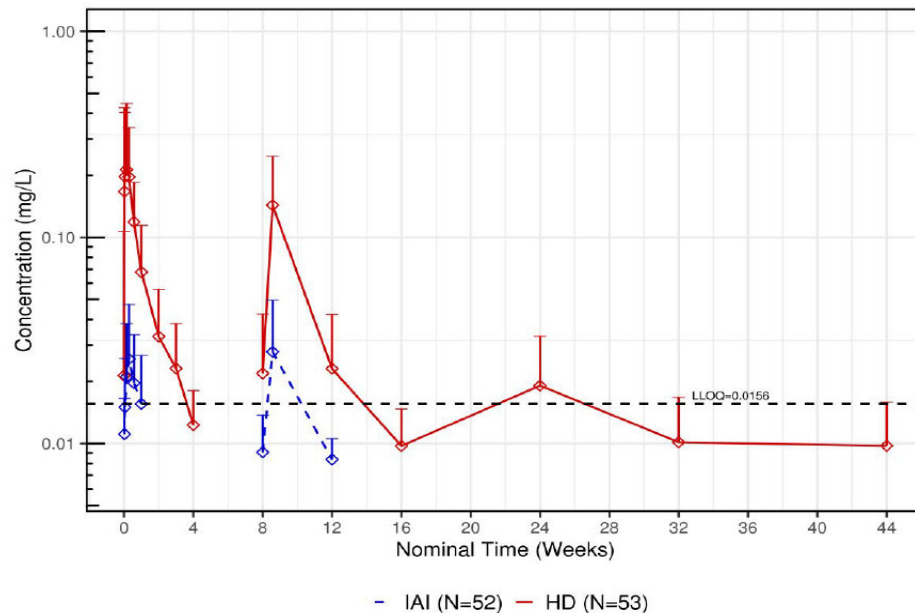
Note: All PK parameters were calculated for the first dosing interval with the exception of C_{trough} (Week 12)/ C_{trough} (Week 4).

/home (b) (6) sasdata/Data/Production/PK/VGFT/VGFT-HD-AMD/VGFTe-AMD-1905/Final/Analysis_CSR/Programs/Generated/T_PPSUMFR.sas (b) (6) 18JUL2022 16:13 SAS 9.4)

Source: Table 6 of Study CANDELA Clinical Pharmacology Report

Free aflibercept in all subjects

Figure 6. Mean (+SD) concentrations of free aflibercept in plasma by nominal time and treatment group in patients with nAMD (Study CANDELA, log-scaled)

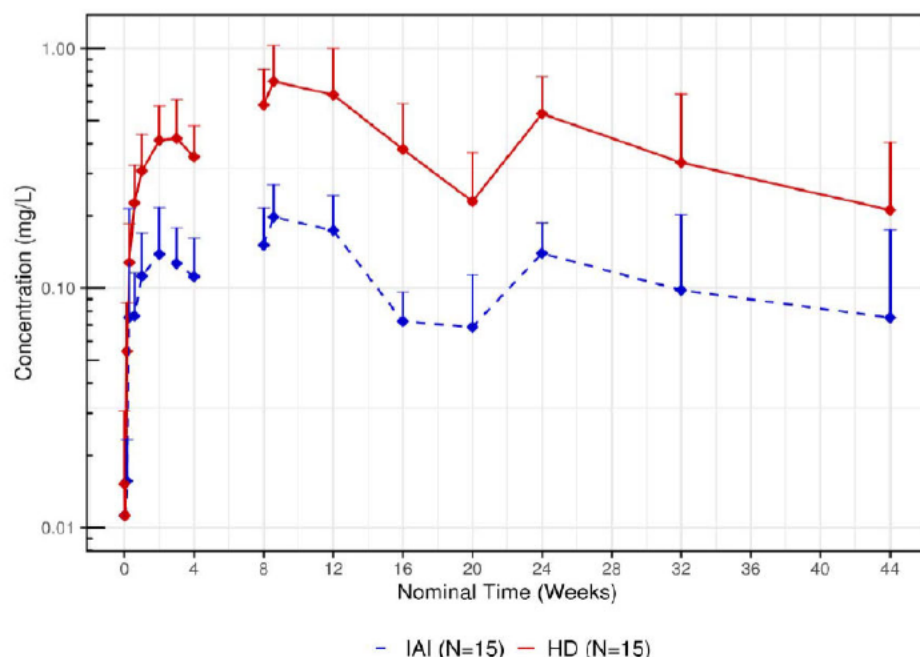


N = Number of patients; SD = Standard deviation; IAI = Intravitreal aflibercept injection; HD = High-dose aflibercept injection
 Note: Concentrations below the lower limit of quantification (LLOQ) were set to LLOQ/2.
 Data/Development/PK/VGFT/VGFT-HD-AMD/VGFTc-AMD-1905/Interim/Analysis_CSR/Programs/TFL/Figures/F_PCMNLOGFR.sas (&_metauser 2022-07-15 14:20:34 SAS Linux 9.4).

Source: Figure 1 of Study CANDELA Clinical Pharmacology Report

Adjusted bound aflibercept in dense PK substudy

Figure 7. Mean (+SD) concentrations of adjusted bound aflibercept in plasma by nominal time and treatment group in patients with nAMD (Study CANDELA, log-scaled, dense PK substudy)



N = Number of patients; SD = Standard deviation; IAI = Intravitreal aflibercept injection; HD = High-dose aflibercept injection
 Note: Concentrations below the lower limit of quantification (LLOQ) were set to LLOQ/2.
 Adjusted bound aflibercept = 0.717*bound aflibercept.
 /Data/Development/PK/VGFT/VGFT-HD-AMD/VGFTe-AMD-
 1905/Interim/Analysis_CSR/Programs/TFL/Figures/F_PCMNLOGSUBBO.sas (&_metauser 2022-07-15 14:01:46 SAS Linux
 9.4).

Source: Figure 5 of Study CANDELA Clinical Pharmacology Report

Table 13. Summary of PK parameters of adjusted bound aflibercept in plasma by treatment group in patients with nAMD (Study CANDELA, dense PK substudy)

		IAI (N=15)				HD (N=15)			
PK Parameters	Unit	n	Mean (SD)	Median	Min : Max	n	Mean (SD)	Median	Min : Max
AUC _{inf}	day*mg/L	0				0			
AUC _{inf} /Dose	day*mg/L/mg	0				0			
AUC _{last}	day*mg/L	15	2.93 (1.51)	2.79	0.567 : 5.94	15	9.45 (3.58)	10.0	2.41 : 15.3
AUC _{last} /Dose	day*mg/L/mg	15	1.46 (0.754)	1.39	0.283 : 2.97	15	1.18 (0.447)	1.25	0.301 : 1.91
AUC ₀₋₂₈	day*mg/L	6	2.24 (0.612)	2.32	1.35 : 2.85	8	9.81 (3.33)	11.1	5.56 : 12.8
C _{max}	mg/L	15	0.177 (0.131)	0.138	0.0731 : 0.571	15	0.456 (0.173)	0.480	0.116 : 0.774
C _{max} /Dose	mg/L/mg	15	0.0885 (0.0655)	0.0692	0.0366 : 0.285	15	0.0569 (0.0216)	0.0600	0.0145 : 0.0968
C _{last}	mg/L	15	0.115 (0.0502)	0.103	0.0496 : 0.218	15	0.353 (0.123)	0.366	0.116 : 0.564
C _{trough} (Week 12)/ C _{trough} (Week 4)		14	1.67 (0.580)	1.65	0.893 : 3.31	15	1.82 (0.652)	1.80	0.276 : 2.87
t _{1/2}	day	0				2	30.0 (---)	30.0	28.5 : 31.5
t _{max}	day	15	--	14.1	1.92 : 21.1	15	--	21.0	6.96 : 28.1
t _{last}	day	15	--	28.0	6.94 : 30.1	15	--	28.0	27.9 : 29.0

N = Number of patients; n = Number of patients contributing to each PK parameter; SD = Standard deviation; IAI = Intravitreal aflibercept injection; HD = High-dose aflibercept injection

Note: All PK parameters were calculated for the first dosing interval with the exception of C_{trough} (Week 12)/ C_{trough} (Week 4).

Adjusted bound aflibercept = 0.717*bound aflibercept.

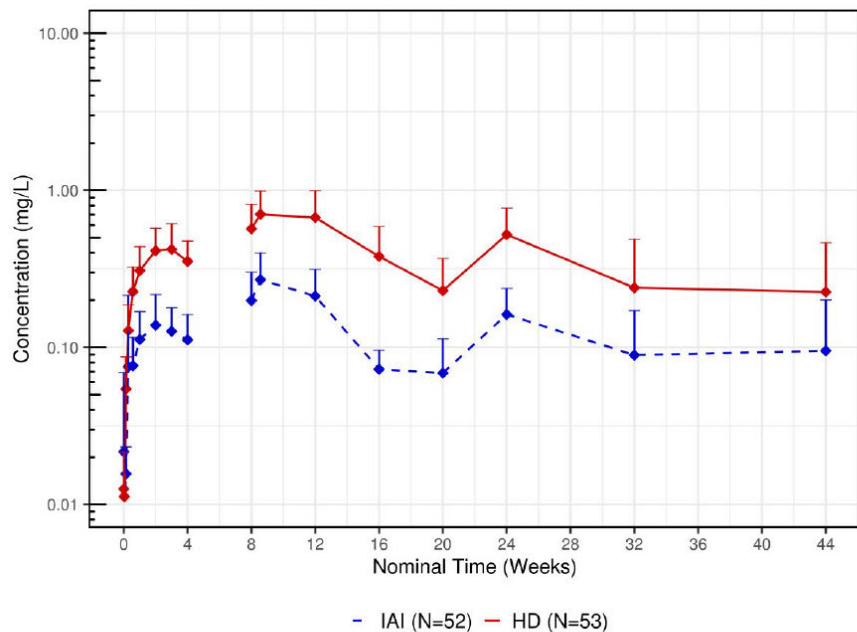
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1905/Final/Analysis_CSR/Programs/Generated/T_PPSUMBO.sas (b) (6) 18JUL2022 16:18 SAS 9.4)

Source: Table 7 of Study CANDELA Clinical Pharmacology Report

Adjusted bound aflibercept in all subjects

Figure 8. Mean (+SD) concentrations of adjusted bound aflibercept in plasma by nominal time and treatment group in patients with nAMD (Study CANDELA, log-scaled)

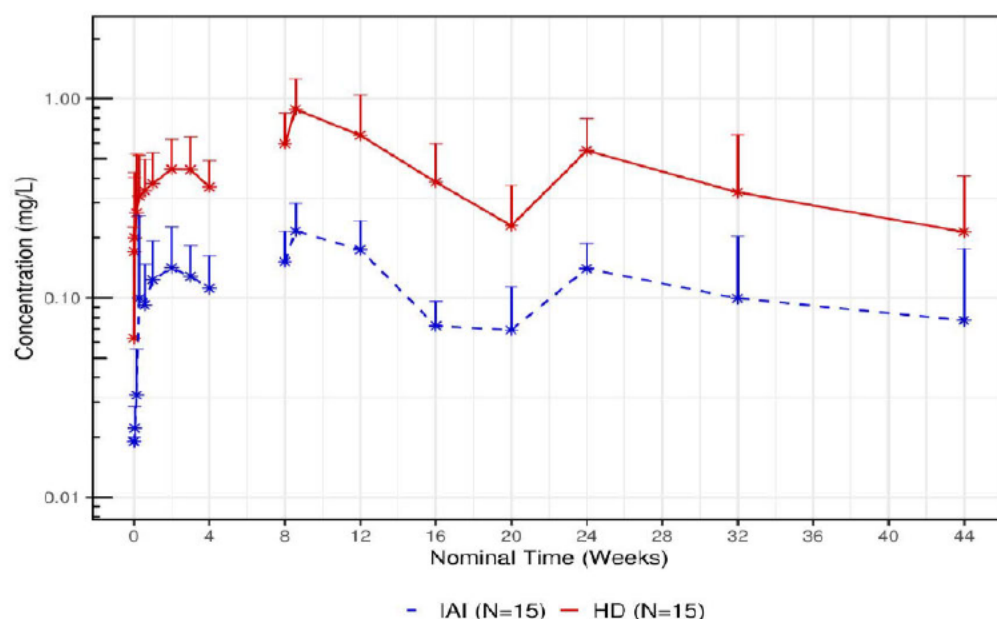


N = Number of patients; SD = Standard deviation; IAI = Intravitreal aflibercept injection; HD = High-dose aflibercept injection
Note: Concentrations below the lower limit of quantification (LLOQ) were set to LLOQ/2.
Adjusted bound aflibercept = 0.717*bound aflibercept.
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Source: Figure 2 of Study CANDELA Clinical Pharmacology Report

Total aflibercept in dense PK substudy

Figure 9. Mean (+SD) concentrations of total aflibercept in plasma by nominal time and treatment group in patients with nAMD (Study CANDELA, log-scaled, dense PK substudy)



N = Number of patients; SD = Standard deviation; IAI = Intravitreal aflibercept injection; HD = High-dose aflibercept injection
 Note: Concentrations below the lower limit of quantification (LLOQ) were set to LLOQ/2.
 Adjusted bound aflibercept = 0.717*bound aflibercept. Total aflibercept = Sum of adjusted bound aflibercept + free aflibercept.
 /Data/Development/PK/VGFT/VGFT-HD-AMD/VGFTc-AMD-1905/Interim/Analysis_CSR/Programs/TFL/Figures/F_PCMNLOGSUBTO.sas (&_metauser 2022-07-15 14:01:06 SAS Linux 9.4).

Source: Figure 6 of Study CANDELA Clinical Pharmacology Report

Table 14. Summary of PK parameters of total aflibercept in plasma by treatment group in patients with nAMD (Study CANDELA, dense PK substudy)

PK Parameters	Unit	IAI (N=15)				HD (N=15)			
		n	Mean (SD)	Median	Min : Max	n	Mean (SD)	Median	Min : Max
AUC _{inf}	day*mg/L	0				0			
AUC _{inf} /Dose	day*mg/L/mg	0				0			
AUC _{last}	day*mg/L	15	3.09 (1.67)	2.90	0.771 : 6.72	15	11.1 (4.33)	12.2	2.48 : 18.3
AUC _{last} /Dose	day*mg/L/mg	15	1.55 (0.837)	1.45	0.386 : 3.36	15	1.39 (0.541)	1.52	0.310 : 2.29
AUC ₀₋₂₈	day*mg/L	8	2.82 (1.21)	2.81	1.35 : 5.27	9	11.6 (3.59)	12.6	6.53 : 15.1
C _{max}	mg/L	15	0.187 (0.152)	0.143	0.0731 : 0.657	15	0.541 (0.219)	0.568	0.116 : 0.953
C _{max} /Dose	mg/L/mg	15	0.0936 (0.0762)	0.0717	0.0366 : 0.328	15	0.0677 (0.0273)	0.0710	0.0145 : 0.119
C _{last}	mg/L	15	0.117 (0.0521)	0.103	0.0496 : 0.218	15	0.361 (0.130)	0.379	0.116 : 0.583
C _{trough} (Week 12)/ C _{trough} (Week 4)		14	1.67 (0.580)	1.65	0.893 : 3.31	15	1.82 (0.658)	1.82	0.263 : 2.92
t _{1/2}	day	1	26.3 (---)	26.3	26.3 : 26.3	2	28.7 (---)	28.7	25.8 : 31.5
t _{max}	day	15	--	14.0	1.92 : 21.1	15	--	21.0	0.147 : 27.9
t _{last}	day	15	--	28.0	6.94 : 30.1	15	--	28.0	27.9 : 29.0

N = Number of patients; n = Number of patients contributing to each PK parameter; SD = Standard deviation; IAI = Intravitreal aflibercept injection; HD = High-dose aflibercept injection

Note: All PK parameters were calculated for the first dosing interval with the exception of C_{trough} (Week 12)/ C_{trough} (Week 4).

Total aflibercept = Sum of adjusted bound aflibercept + free aflibercept.

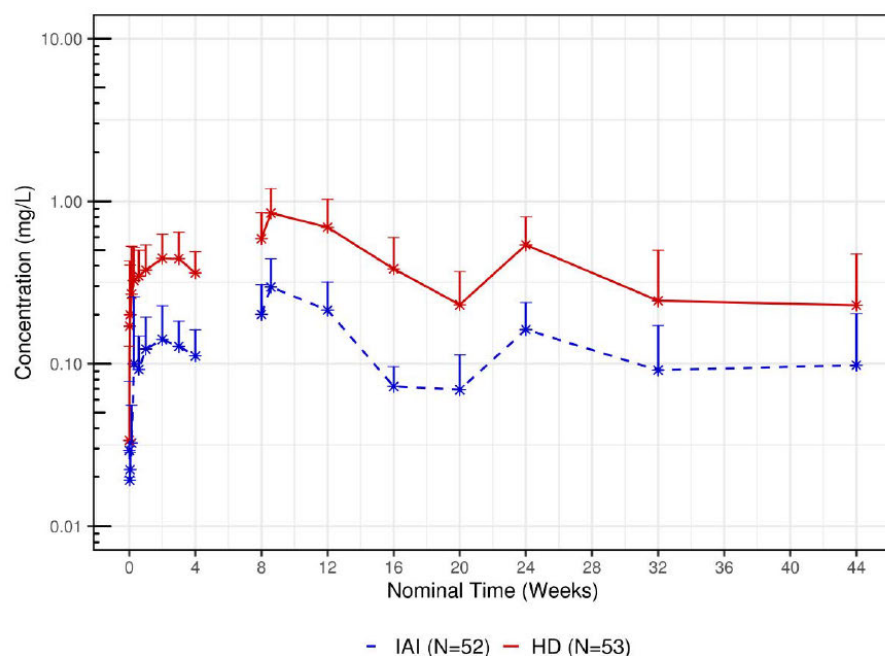
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1905/Final/Analysis_CSR/Programs/Generated/T_PPSUMTO.sas (b) (6) 18JUL2022 16:10 SAS 9.4)

Source: Table 8 of Study CANDELA Clinical Pharmacology Report

Total aflibercept in all subjects

Figure 10. Mean (+SD) concentrations of total aflibercept in plasma by nominal time and treatment group in patients with nAMD (Study CANDELA, log-scaled)



N = Number of patients; SD = Standard deviation; IAI = Intravitreal aflibercept injection; HD = High-dose aflibercept injection
 Note: Concentrations below the lower limit of quantification (LLOQ) were set to LLOQ/2.
 Adjusted bound aflibercept = 0.717*bound aflibercept. Total aflibercept = Sum of adjusted bound aflibercept + free aflibercept.
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Source: Figure 3 of Study CANDELA Clinical Pharmacology Report

Immunogenicity assessment

None

4.2.2 Phase 2/3 Study VGFTe-HD-DME-1934 (PHOTON)

Title: A Randomized, Double-Masked, Active-Controlled Phase 2/3 Study of the Efficacy and Safety of High-Dose Aflibercept in Patients with Diabetic Macular Edema

Study period: 29 Jun 2020 - 30 May 2022

Objectives:

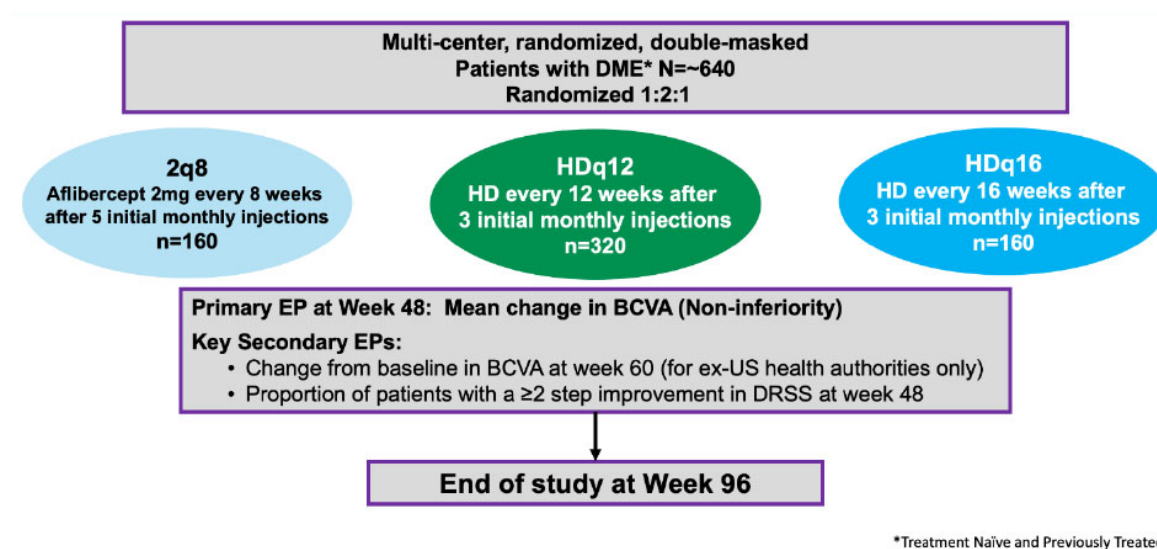
- Primary: efficacy
- Secondary: efficacy, PK

Study design: This is the week 48 analysis of an ongoing Phase 2/3, multi-center, randomized, double-masked study in participants with DME involving the center of the macula that investigates the efficacy and safety of HD (8 mg) aflibercept versus 2 mg aflibercept. The study consists of a screening/baseline period, a treatment period, and an end of study visit at week 96 (Figure 1). A

total of approximately 640 eligible participants were planned to be randomized into 3 treatment groups in a 1:2:1 ratio as follows:

- 2q8: 2 mg aflibercept every 8 weeks, following 5 initial monthly doses (n=160),
- HDq12: HD aflibercept every 12 weeks, following 3 initial monthly doses (n=320),
- HDq16: HD aflibercept every 16 weeks, following 3 initial monthly doses (n=160).

Figure 11. Study design (Study PHOTON)



Abbreviations: 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HD=high dose aflibercept (8 mg aflibercept); HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; BCVA=Best corrected visual acuity; DME=diabetic macular edema; EP=Endpoint; DRSS=Diabetic Retinopathy Severity Scale.

Note: An extension period (protocol amendment 5) is currently in the process of being implemented which will continue follow-up of participants through week 156.

Source: Figure 1 of Study PHOTON CSR

Test Drug Product

Treatment Name	Aflibercept		Sham
Group Name	HD Aflibercept	Aflibercept	
Type	Biologic	Biologic	Placebo
Dose Formulation	Liquid formulation	Liquid formulation	N/A
Unit Dose Strength(s)	114.3 mg/mL	40 mg/mL	N/A
Dosage Level(s)	8 mg (70 µL)	2 mg (50 µL)	N/A
Route of Administration	IVT		Mock IVT injection (syringe without needle)
Frequency	HDq12, HDq16 after 3 initial monthly injections	2q8 after 5 initial monthly injections	Administration schedule same as active treatment
Use	Experimental	Active-comparator (control)	N/A
IMP and NIMP	IMP	IMP	N/A
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Syringes supplied by the study site
Packaging and Labeling	Study drug was provided as liquid formulation in a vial. Each vial was labeled as required per country requirement	Study drug was provided as liquid formulation in a vial. Each vial was labeled as required per country requirement	N/A
Alias	None	EYLEA	N/A

HD=High dose aflibercept (8 mg aflibercept); 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HD=high dose aflibercept (8 mg aflibercept); HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; IMP=Investigational Medicinal Product; IVT=Intravitreal; N/A=Not applicable; NIMP=Non-Investigational Medicinal Product.

Source: Table 2 of Study PHOTON CSR

PK and Immunogenicity Sampling

In all participants, blood samples for PK analysis and antidrug antibodies (ADA) were obtained at baseline on Day 1, and Weeks 4, 12, 28, 48, 96 (EOS, immunogenicity only).

Approximately 24 participants were planned to be included in a dense PK sub-study (n=8 per group, with half Japanese and half non-Japanese per group).

Table 15. PK sampling schedule for dense PK substudy (Study PHOTON)

Visit	Dose	Assessment Day	Assessment Time (h)	PK Sample	Heart Rate and Blood Pressure ³
Screening 2 ¹		-20 to -1	±2h		X ²
Visit 2	X	1	Predose ³	X	X ²
			4h ±30min	X	
			8h ±2h	X	
		2	±2h ³	X	X ²
		3	±2h ³	X	X ²
		5	±2h ³	X	X ²
		8	±2h ³	X	X ²
		15	±2h ³	X	X ²
		22	±2h ³	X	X ²

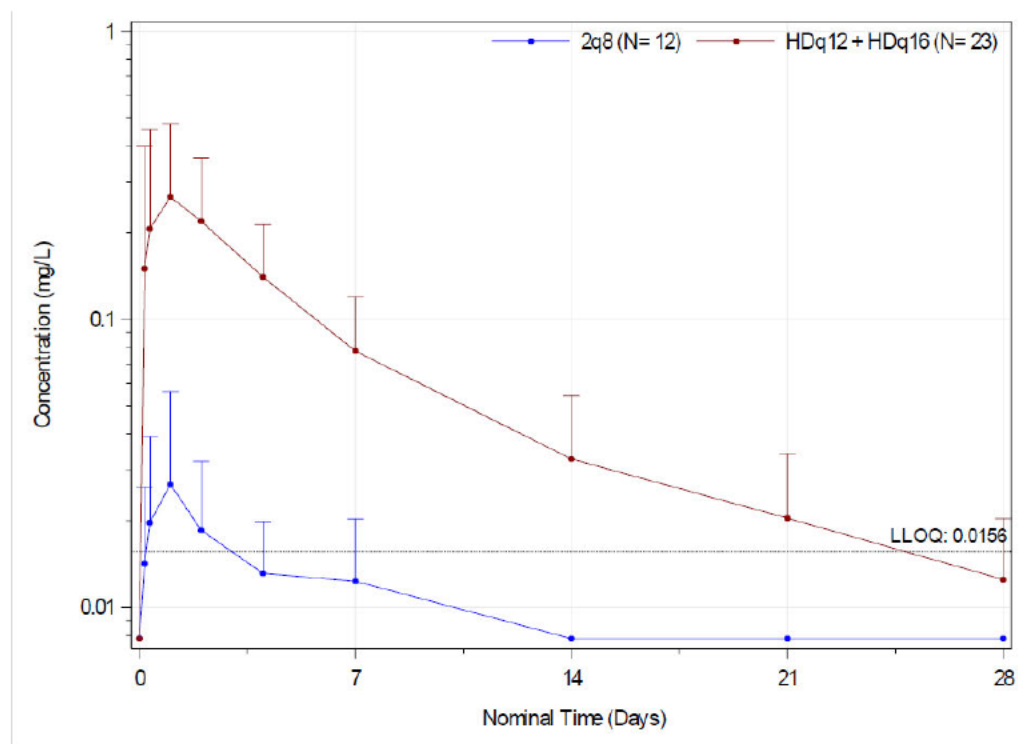
Source: Table 3 of Protocol VGFTe-HD-DME-1934 Amendment 4

PK Results

The PK profiles and PK parameters of free, adjusted, and total aflibercept in plasma are shown as below.

Free aflibercept in dense PK substudy

Figure 12. Mean (+SD) concentrations of free aflibercept in plasma by nominal time and treatment in participants with DME with unilateral treatment in the dense PK sampling substudy (Study PHOTON, log-scaled)



Treatment Group	D0	D0H4	D0H8	D1	D2	D4	D7	D14	D21	D28
2q8	11	12	11	12	12	12	12	12	12	12
HDq12 + HDq16	23	22	22	22	22	22	19	21	21	21

N = Number of participants; SD = Standard deviation; DME = Diabetic macular edema; 2q8 = 2 mg intravitreal aflibercept every 8 weeks following 5 initial monthly doses; HDq12 = High-dose (8 mg) intravitreal aflibercept every 12 weeks following 3 initial monthly doses; HDq16 = High-dose (8 mg) intravitreal aflibercept every 16 weeks following 3 initial monthly doses; LLOQ = Lower limit of quantitation; D = Day; H = Hour

Note: Table under the figure presents the number of participants contributing to the statistics for the corresponding visits/timepoints and treatments. Concentrations below the LLOQ were set to LLOQ/2. HDq12+HDq16 = combined data from treatment groups HDq12 and HDq16. Participants in the dense PK substudy only received aflibercept injections unilaterally.

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Source: Figure 1 of Study PHOTON Clinical Pharmacology Report

Table 16. Summary of PK parameters of free aflibercept in plasma by treatment in participants with DME with unilateral treatment in the dense PK sampling substudy (Study PHOTON)

		2q8 (N=12)				HDq12+HDq16 (N=23)			
PK									
Parameters	Unit	n	Mean (SD)	Median	Min : Max	n	Mean (SD)	Median	Min : Max
AUC _{inf}	day*mg/L	0				13	2.26 (0.714)	2.29	1.14 : 3.36
AUC _{inf} /Dose	day*mg/L/mg	0				13	0.283 (0.0892)	0.287	0.143 : 0.420
AUC _{last}	day*mg/L	7	0.126 (0.0660)	0.146	0.0244 : 0.202	21	1.71 (0.816)	1.85	0.230 : 2.82
AUC _{last} /Dose	day*mg/L/mg	7	0.0628 (0.0330)	0.0732	0.0122 : 0.101	21	0.214 (0.102)	0.232	0.0287 : 0.352
AUC ₀₋₂₈	day*mg/L	6	0.170 (0.124)	0.162	0 : 0.358	19	1.86 (0.840)	1.97	0 : 2.89
C _{max}	mg/L	12	0.0266 (0.0333)	0.0198	0 : 0.109	23	0.310 (0.263)	0.245	0 : 1.08
C _{max} /Dose	mg/L/mg	12	0.0133 (0.0167)	0.00990	0 : 0.0545	23	0.0388 (0.0328)	0.0306	0 : 0.135
C _{last}	mg/L	7	0.0217 (0.00619)	0.0195	0.0157 : 0.0335	21	0.0390 (0.0399)	0.0223	0.0158 : 0.169
C _{trough28}	mg/L	12	0 (0)	0	0 : 0	21	0.00730 (0.0113)	0	0 : 0.0371
t _{1/2}	day	1	17.3 (---)	17.3	17.3 : 17.3	15	8.43 (4.55)	8.48	1.41 : 20.4
t _{max}	day	12	--	0.268	0 : 7.04	23	--	0.965	0 : 4.01
t _{last}	day	7	--	6.94	1.98 : 7.04	21	--	20.9	2.00 : 32.0

PK= Pharmacokinetic; N = Number of participants; n = Number of participants contributing to each PK parameter;
SD = Standard deviation; DME = Diabetic macular edema; 2q8 = 2 mg intravitreal aflibercept every 8 weeks following 5 initial monthly doses; HDq12 = High-dose (8 mg) intravitreal aflibercept every 12 weeks following 3 initial monthly doses;
HDq16 = High-dose (8 mg) intravitreal aflibercept every 16 weeks following 3 initial monthly doses
Note: HDq12+HDq16 = combined data from treatment groups HDq12 and HDq16. Participants in the dense PK substudy only received aflibercept injections unilaterally. Data presented were collected during the dense PK substudy (from predose Day 0 through Day 28).

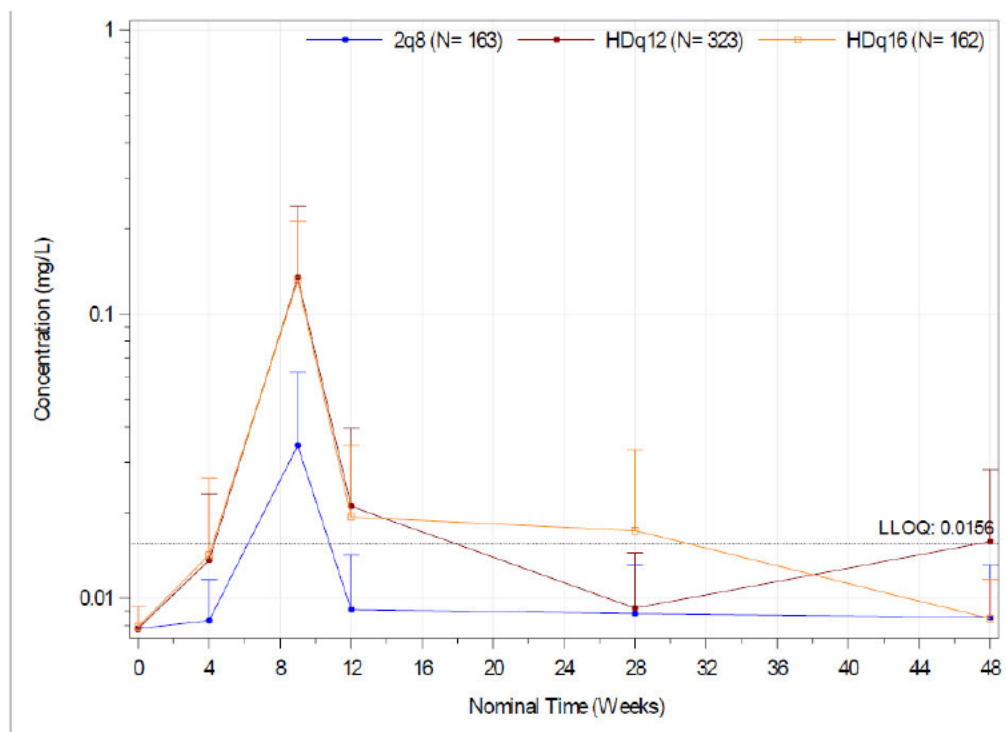
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1934/InterimWK48/Analysis CSR/Programs/TFL/Tables/Generated/T PPSUMF.sas (b) (6) 27OCT2022 21:17 SAS 9.4)

Source: Table 7 of Study PHOTON Clinical Pharmacology Report

Free aflibercept in all subjects

Figure 13. Mean (+SD) concentrations of free aflibercept in plasma by nominal time and treatment group in participants with DME in the sparse PK sampling study (Study PHOTON, log-scaled)



Treatment Group	WEEK0	WEEK4	WEEK9	WEEK12	WEEK28	WEEK48
2q8	150	143	34	152	140	137
HDq12	283	286	47	299	278	253
HDq16	135	134	25	150	138	140

N = Number of participants; SD = Standard deviation; DME = Diabetic macular edema; 2q8 = 2 mg intravitreal aflibercept every 8 weeks following 5 initial monthly doses; HDq12 = High-dose (8 mg) intravitreal aflibercept every 12 weeks following 3 initial monthly doses; HDq16 = High-dose (8 mg) intravitreal aflibercept every 16 weeks following 3 initial monthly doses; LLOQ = Lower limit of quantitation

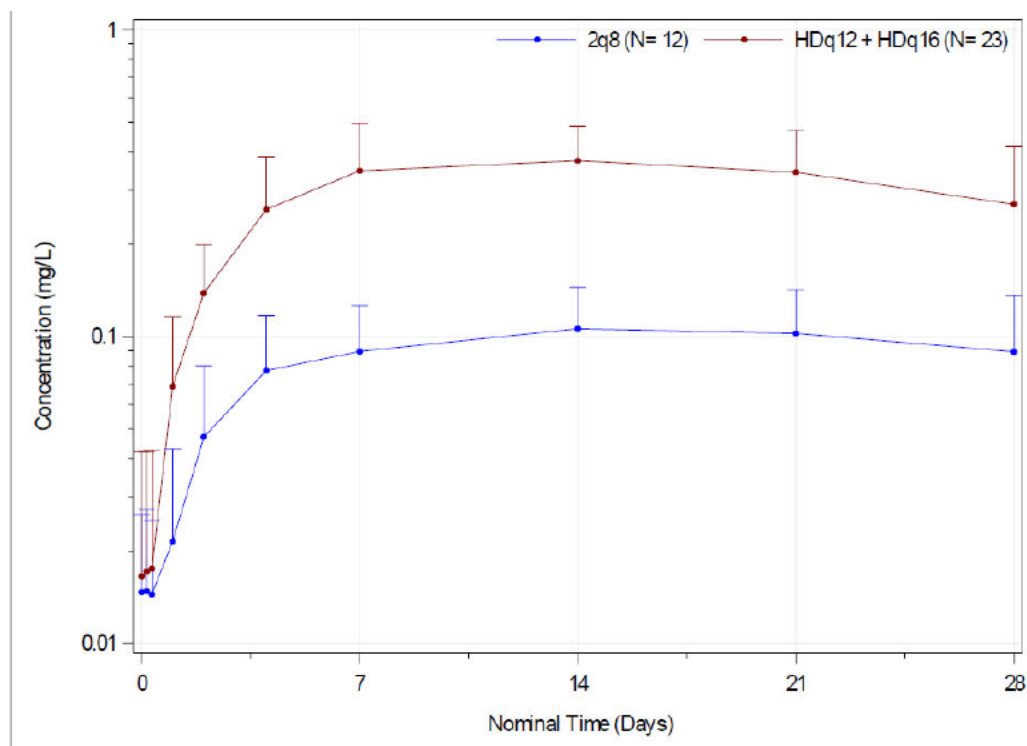
Note: Table under the figure presents the number of participants contributing to the statistics for the corresponding visits/timepoints and treatment groups. Concentrations below the LLOQ were set to LLOQ/2. Post dose samples and samples collected during the dense PK substudy (from post dose on Day 0 through Day 21) were excluded.

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Source: Figure 4 of Study PHOTON Clinical Pharmacology Report

Adjusted bound aflibercept in dense PK substudy

Figure 14. Mean (+SD) Concentrations of adjusted bound aflibercept in plasma by nominal time and treatment in participants with DME with unilateral treatment in the dense PK sampling substudy (Study PHOTON, log-scaled)



Treatment Group	D0	D0H4	D0H8	D1	D2	D4	D7	D14	D21	D28
2q8	11	12	11	12	12	12	12	12	12	12
HDq12 + HDq16	23	22	22	22	22	22	19	21	21	21

N = Number of participants; SD = Standard deviation; DME = Diabetic macular edema; 2q8 = 2 mg intravitreal aflibercept every 8 weeks following 5 initial monthly doses; HDq12 = High-dose (8 mg) intravitreal aflibercept every 12 weeks following 3 initial monthly doses; HDq16 = High-dose (8 mg) intravitreal aflibercept every 16 weeks following 3 initial monthly doses; LLOQ = Lower limit of quantitation; D = Day; H = Hour
Note: Table under the figure presents the number of participants contributing to the statistics for the corresponding visits/timepoints and treatments. Concentrations below the LLOQ were set to LLOQ/2. Adjusted bound aflibercept = 0.717*bound aflibercept. HDq12+HDq16 = combined data from treatment groups HDq12 and HDq16. Participants in the dense PK substudy only received aflibercept injections unilaterally.
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Source: Figure 2 of Study PHOTON Clinical Pharmacology Report

Table 17. Summary of PK parameters of adjusted bound aflibercept in plasma by treatment in participants with DME with unilateral treatment in the dense PK sampling substudy (Study PHOTON)

		2q8 (N=12)				HDq12+HDq16 (N=23)			
PK Parameters	Unit	n	Mean (SD)	Median	Min : Max	n	Mean (SD)	Median	Min : Max
AUC _{inf}	day*mg/L	0				0			
AUC _{inf} /Dose	day*mg/L/mg	0				0			
AUC _{last}	day*mg/L	11	2.48 (0.607)	2.52	1.33 : 3.67	23	8.30 (3.05)	8.03	4.07 : 17.6
AUC _{last} /Dose	day*mg/L/mg	11	1.24 (0.303)	1.26	0.664 : 1.83	23	1.04 (0.382)	1.00	0.509 : 2.20
AUC ₀₋₂₈	day*mg/L	4	2.53 (0.360)	2.49	2.14 : 3.00	14	8.71 (3.65)	8.42	3.27 : 17.7
C _{max}	mg/L	12	0.115 (0.0442)	0.124	0 : 0.154	23	0.387 (0.135)	0.380	0.137 : 0.774
C _{max} /Dose	mg/L/mg	12	0.0575 (0.0221)	0.0618	0 : 0.0771	23	0.0483 (0.0168)	0.0475	0.0171 : 0.0968
C _{last}	mg/L	11	0.104 (0.0314)	0.0961	0.0551 : 0.154	23	0.287 (0.136)	0.260	0.0649 : 0.599
C _{trough28}	mg/L	12	0.0873 (0.0506)	0.0929	0 : 0.154	21	0.269 (0.149)	0.252	0 : 0.599
t _{max}	day	12	--	14.0	0 : 23.9	23	--	14.0	3.96 : 37.1
t _{last}	day	11	--	27.0	21.0 : 30.1	23	--	27.9	20.9 : 43.0

PK= Pharmacokinetic; N = Number of participants; n = Number of participants contributing to each PK parameter;
SD = Standard deviation; DME = Diabetic macular edema; 2q8 = 2 mg intravitreal aflibercept every 8 weeks following 5 initial monthly doses; HDq12 = High-dose (8 mg) intravitreal aflibercept every 12 weeks following 3 initial monthly doses;
HDq16 = High-dose (8 mg) intravitreal aflibercept every 16 weeks following 3 initial monthly doses
Note: Adjusted bound aflibercept = 0.717*bound aflibercept. HDq12+HDq16 = combined data from treatment groups HDq12 and HDq16. Participants in the dense PK substudy only received aflibercept injections unilaterally. Data presented were collected during the dense PK substudy (from predose Day 0 through Day 28).

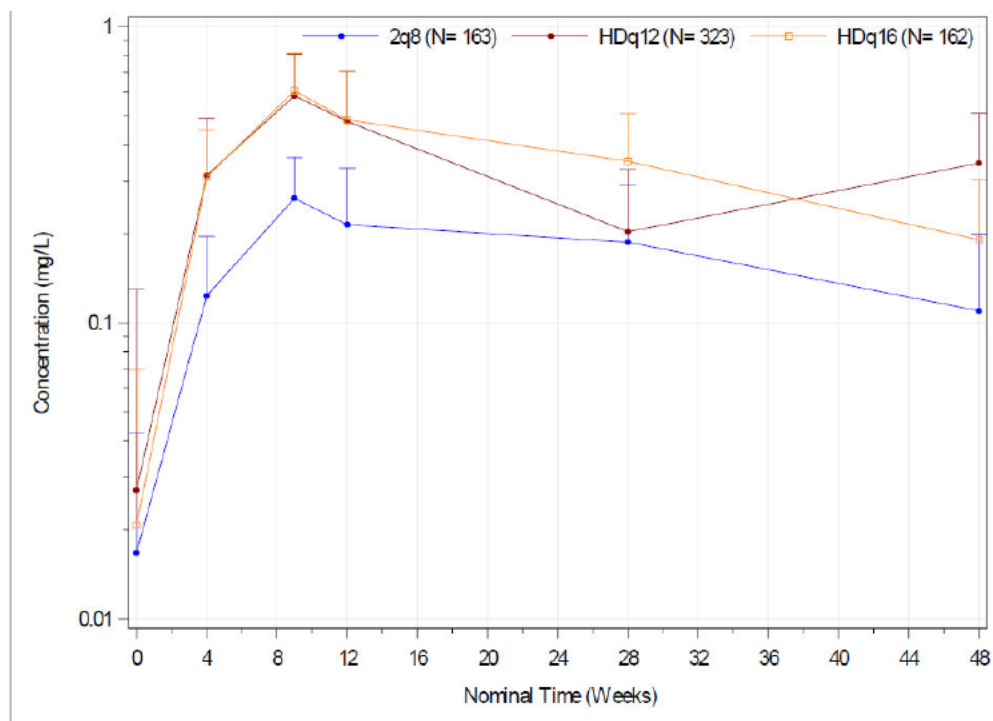
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1934/InterimWK48/Analysis_CSR/Programs/TFL/Tables/Generated/T_PPSUMADJ.sas (b) (6) 27OCT2022 21:17 SAS 9.4)

Source: Table 8 of Study PHOTON Clinical Pharmacology Report

Adjusted bound aflibercept in all subjects

Figure 15. Mean (+SD) concentrations of adjusted bound aflibercept in plasma by nominal time and treatment group in participants with DME in the sparse PK sampling study (Study PHOTON, log-scaled)



Treatment Group	WEEK0	WEEK4	WEEK9	WEEK12	WEEK28	WEEK48
2q8	150	143	34	152	140	137
HDq12	283	286	47	299	278	253
HDq16	135	134	25	150	138	140

N = Number of participants; SD = Standard deviation; DME = Diabetic macular edema; 2q8 = 2 mg intravitreal aflibercept every 8 weeks following 5 initial monthly doses; HDq12 = High-dose (8 mg) intravitreal aflibercept every 12 weeks following 3 initial monthly doses; HDq16 = High-dose (8 mg) intravitreal aflibercept every 16 weeks following 3 initial monthly doses; LLOQ = 1/4 Lower limit of quantitation

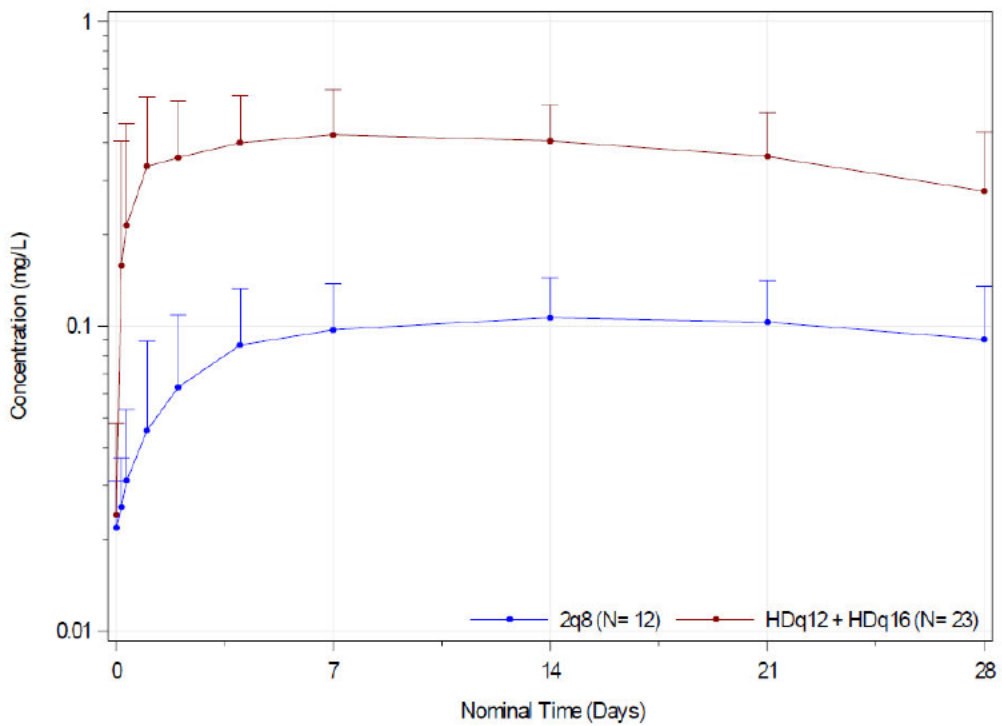
Note: Table under the figure presents the number of participants contributing to the statistics for the corresponding visits/timepoints and treatment groups. Concentrations below the LLOQ were set to LLOQ/2. Adjusted bound aflibercept = 0.717*bound aflibercept. Post dose samples and samples collected during the dense PK substudy (from post dose on Day 0 through Day 21) were excluded.

/sasdata/Data/Production/PK/VGFT/VGFT-HD-DME/VGFTe-DME-1934/InterimWK48/Analysis_CSR/Programs/TFL/Figures/F_PCMNLOGADJ.sas (b) (6) 27OCT22:20:46 SAS Linux 9.4)

Source: Figure 5 of Study PHOTON Clinical Pharmacology Report

Total aflibercept in dense PK substudy

Figure 16. Mean (+SD) concentrations of total aflibercept in plasma by nominal time and treatment in participants with DME with unilateral treatment in the dense PK sampling substudy (Study PHOTON, log-scaled)



Treatment Group	D0	D0H4	D0H8	D1	D2	D4	D7	D14	D21	D28
2q8	11	12	11	12	12	12	12	12	12	12
HDq12 + HDq16	23	22	22	22	22	22	19	21	21	21

N = Number of participants; SD = Standard deviation; DME = Diabetic macular edema; 2q8 = 2 mg intravitreal aflibercept every 8 weeks following 5 initial monthly doses; HDq12 = High-dose (8 mg) intravitreal aflibercept every 12 weeks following 3 initial monthly doses; HDq16 = High-dose (8 mg) intravitreal aflibercept every 16 weeks following 3 initial monthly doses; LLOQ = Lower limit of quantitation; D = Day; H = Hour

Note: Table under the figure presents the number of participants contributing to the statistics for the corresponding visits/timpoints and treatments. Concentrations below the LLOQ were set to LLOQ/2. Adjusted bound

aflibercept = 0.717*bound aflibercept. Total aflibercept = sum of adjusted bound aflibercept and free aflibercept.

HDq12+HDq16 = combined data from treatment groups HDq12 and HDq16. Participants in the dense PK substudy only received aflibercept injections unilaterally.

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1934/InterimWK48/Analysis_CSR/Programs/TFL/Figures/F_PCMNLOGTPKS.sas (b) (6) :27OCT22:20:46 SAS Linux 9.4)

Source: Figure 3 of Study PHOTON Clinical Pharmacology Report

Table 18. Summary of PK parameters of total aflibercept in plasma by treatment in participants with DME with unilateral treatment in the dense PK sampling substudy (Study PHOTON)

		2q8 (N=12)				HDq12+HDq16 (N=23)			
PK									
Parameters	Unit	n	Mean (SD)	Median	Min : Max	n	Mean (SD)	Median	Min : Max
AUC _{inf}	day*mg/L	0				1	13.1 (---)	13.1	13.1 : 13.1
AUC _{inf} /Dose	day*mg/L/mg	0				1	1.64 (---)	1.64	1.64 : 1.64
AUC _{last}	day*mg/L	11	2.60 (0.681)	2.55	1.33 : 3.88	23	10.1 (3.62)	10.4	4.07 : 19.8
AUC _{last} /Dose	day*mg/L/mg	11	1.30 (0.341)	1.27	0.664 : 1.94	23	1.27 (0.453)	1.29	0.509 : 2.47
AUC ₀₋₂₈	day*mg/L	5	2.92 (0.717)	2.67	2.25 : 4.01	17	10.6 (3.85)	10.5	4.00 : 19.8
C _{max}	mg/L	12	0.118 (0.0464)	0.124	0 : 0.168	23	0.505 (0.217)	0.469	0.230 : 1.08
C _{max} /Dose	mg/L/mg	12	0.0588 (0.0232)	0.0618	0 : 0.0842	23	0.0632 (0.0272)	0.0586	0.0288 : 0.135
C _{last}	mg/L	11	0.104 (0.0314)	0.0961	0.0551 : 0.154	23	0.295 (0.145)	0.260	0.0649 : 0.616
C _{trough28}	mg/L	12	0.0873 (0.0506)	0.0929	0 : 0.154	21	0.276 (0.158)	0.252	0 : 0.616
t _{max}	day	12	--	14.0	0 : 23.9	23	--	6.97	0.216 : 33.0
t _{last}	day	11	--	27.0	21.0 : 30.1	23	--	27.9	20.9 : 43.0

PK= Pharmacokinetic; N = Number of participants; n = Number of participants contributing to each PK parameter;
SD = Standard deviation; DME = Diabetic macular edema; 2q8 = 2 mg intravitreal aflibercept every 8 weeks following 5 initial monthly doses; HDq12 = High-dose (8 mg) intravitreal aflibercept every 12 weeks following 3 initial monthly doses;
HDq16 = High-dose (8 mg) intravitreal aflibercept every 16 weeks following 3 initial monthly doses
Note: Adjusted bound aflibercept = 0.717*bound aflibercept. Total aflibercept = sum of adjusted bound aflibercept and free aflibercept. HDq12+HDq16 = combined data from treatment groups HDq12 and HDq16. Participants in the dense PK substudy only received aflibercept injections unilaterally. Data presented were collected during the dense PK substudy (from predose Day 0 through Day 28).

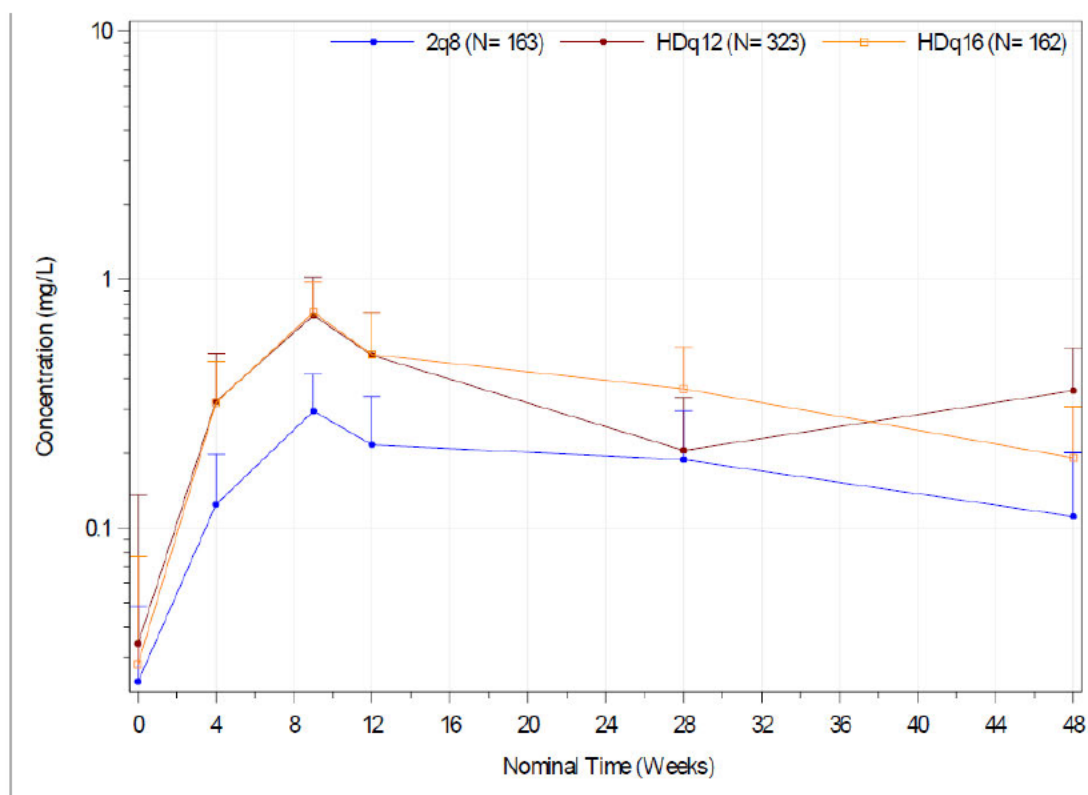
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Source: Table 9 of Study PHOTON Clinical Pharmacology Report

Total aflibercept in all subjects

Figure 17. Mean (+SD) concentrations of total aflibercept in plasma by nominal time and treatment group in participants with DME in the sparse PK sampling study (Study PHOTON, log-scaled)



Treatment Group	WEEK0	WEEK4	WEEK9	WEEK12	WEEK28	WEEK48
2q8	150	143	34	152	140	137
HDq12	283	286	47	299	278	253
HDq16	135	134	25	150	138	140

N = Number of participants; SD = Standard deviation; DME = Diabetic macular edema; 2q8 = 2 mg intravitreal aflibercept every 8 weeks following 5 initial monthly doses; HDq12 = High-dose (8 mg) intravitreal aflibercept every 12 weeks following 3 initial monthly doses; HDq16 = High-dose (8 mg) intravitreal aflibercept every 16 weeks following 3 initial monthly doses; LLOQ = Lower limit of quantitation

Note: Table under the figure presents the number of participants contributing to the statistics for the corresponding visits/timepoints and treatment groups. Concentrations below the LLOQ were set to LLOQ/2. Adjusted bound aflibercept = 0.717*bound aflibercept. Total aflibercept = sum of adjusted bound aflibercept and free aflibercept. Post dose samples and samples collected during the dense PK substudy (from post dose on Day 0 through Day 21) were excluded.

/sasdata/Data/Production/PK/VGFT/VGFT-HD-DME/VGFTe-DME-1934/InterimWK48/Analysis_CSR/Programs/TFL/Figures/F_PCMNLOGT.sas (b) (6) 27OCT22:20:46 SAS Linux 9.4

Source: Figure 6 of Study PHOTON Clinical Pharmacology Report

Immunogenicity Assessment

Out of the 541 participants included in the ADA analysis set, 3/137 (2.2%), 10/263 (3.8%), and 2/141 (1.4%) participants had pre-existing immunoreactivity in the 2q8, HDq12, and HDq16 treatment groups, respectively. The incidence of treatment-emergent ADA in the 2q8, HDq12, and HDq16 treatment groups was 0/137 (0%), 3/263 (1.1%), and 2/141 (1.4%), respectively. No treatment-boosted ADA responses were observed. All of the treatment-emergent responses were indeterminate and of low maximum titer, and no NAb positive responses were observed

Table 19. Summary of immunogenicity assessment by treatment group in participants with DME (Study PHOTON)

ADA Status/Category Max. Titer Category NAb Status	Aflibercept			
	2q8 n (%)	HDq12 n (%)	HDq16 n (%)	HDq12+HDq16 n (%)
ADA				
ADA Analysis Set	137 (100%)	263 (100%)	141 (100%)	404 (100%)
Negative	134 (97.8%)	250 (95.1%)	137 (97.2%)	387 (95.8%)
Pre-existing Immunoreactivity	3 (2.2%)	10 (3.8%)	2 (1.4%)	12 (3.0%)
Treatment-Boosted Response	0	0	0	0
Treatment-Emergent Response	0	3 (1.1%)	2 (1.4%)	5 (1.2%)
Persistent	0	0	0	0
Indeterminate	0	3 (1.1%)	2 (1.4%)	5 (1.2%)
Transient	0	0	0	0
TE & TB Maximum Titer Category				
Low (<1,000)	0	3 (1.1%)	2 (1.4%)	5 (1.2%)
Moderate (1,000 to 10,000)	0	0	0	0
High (>10,000)	0	0	0	0
NAb				
NAb Analysis Set	137 (100%)	263 (100%)	141 (100%)	404 (100%)
NAb Negative	137 (100%)	263 (100%)	141 (100%)	404 (100%)
NAb Positive	0	0	0	0

n = Number of participants; TE = Treatment-emergent; TB = Treatment-boosted; DME = Diabetic macular edema; 2q8 = 2 mg intravitreal aflibercept every 8 weeks following 5 initial monthly doses; HDq12 = High-dose (8 mg) intravitreal aflibercept every 12 weeks following 3 initial monthly doses; HDq16 = High-dose (8 mg) intravitreal aflibercept every 16 weeks following 3 initial monthly doses

Note: Percentages are based on ADA analysis set.

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1934/InterimWK48/Analysis_CSR/Programs/TFL/Tables/Generated/T_ADANABALL.sas (b) (6) 27OCT2022 21:16 SAS 9.4)

Source: Table 10 of Study PHOTON Clinical Pharmacology Report

4.2.3 Phase 3 Study 20968 (PULSAR)

Title: Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of High Dose Aflibercept in Patients With Neovascular Age-Related Macular Degeneration

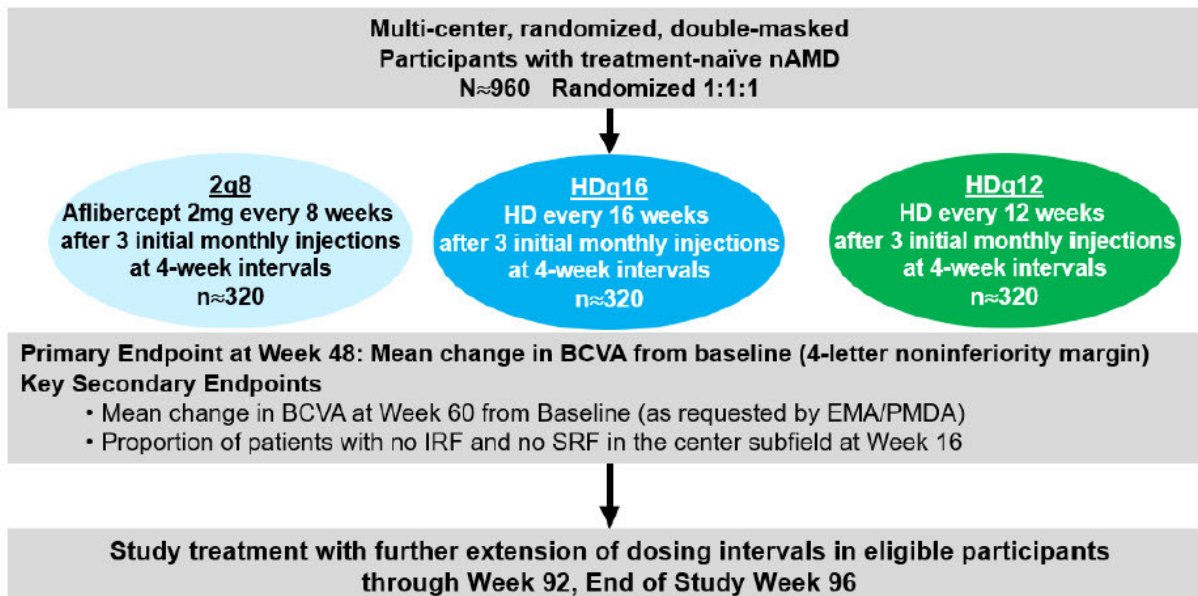
Study period: 20 Aug 2020 - 27 Jul 2022 (ongoing)

Objectives:

- Primary: efficacy
- Secondary: efficacy, safety, PK, immunogenicity

Study design: This is a Phase 3, multi-center, randomized, double-masked, active-controlled study investigating the efficacy, safety, and tolerability of IVT administration of HD aflibercept versus aflibercept 2 mg in participants with treatment-naïve nAMD.

Figure 18. Study design (Study PULSAR)



BCVA = best corrected visual acuity, EMA = European Medicines Agency, HD = high dose, IRF = intraretinal fluid, N = total number of participants, n = number of participants per group, nAMD = neovascular (wet) age-related macular degeneration, PMDA = Pharmaceuticals and Medical Devices Agency, SRF = subretinal fluid
See Definition of terms for treatment group description.

Source: Figure 1 of Study PULSAR CSR

Test drug product

Treatment name	Aflibercept HD	Aflibercept 2 mg	Sham
Type	Drug	Drug	Not applicable
Dose formulation	Solution in vial	Solution in vial	Not applicable
Unit dose strengths	114.3 mg/mL	40 mg/mL	Not applicable
Dosage levels	8 mg (70 µL)	2 mg (50 µL)	Not applicable
Route of administration	IVT injection	IVT injection	Not applicable
Use	Experimental	Active comparator	Sham procedure
Packaging	Sterile 3 mL glass vials	Sterile 2 mL glass vials	Empty kit
Labeling	Each vial was labeled as required per country/region requirement		
Posology	All treatment arms: 3 initial injections at 4-week intervals		
Initiation			
Maintenance	HDq12: every 12 weeks HDq16: every 16 weeks	2q8: every 8 weeks	

Source: Table 7-1 of Study PULSAR CSR

PK Sampling

Sparse PK sampling in all subjects: baseline on Day 1, and Weeks 4, 12, 28, 48,

Dense PK sampling in PK substudy (approximately 12 Japanese participants from Japan sites and 12 non-Asian participants from Europe or US sites) is shown in the Table below:

Table 20. PK sampling schedule for dense PK sub-study (Study PULSAR)

Visit	Dose	Assessment Day	Assessment Time (h)	PK Sample	Heart Rate and Blood Pressure ^a
Screening 2 ^b		-21 to -1	±2h		X
Visit 2 (Baseline)	X	1	Pre-dose ^c	X (pre-injection)	X
			4 ^c	X	
		2	8 ^c	X	
			±2h ^c	X	X
			±2h ^c	X	X
			±2h ^c	X	X
			±2h ^c	X	X
			±2h ^c	X	X
		22	±2h ^c	X	X

AOBP = automated office blood pressure, eCRF = electronic case report form, PK = pharmacokinetics

Participants enrolled in the Dense PK Substudy also had blood pressure and heart rate assessed at each visit within the substudy.

a Timing of all blood pressure assessments had to be within ±2 hours of the clock time of dosing on Day 1. Blood pressure assessments for participants in the Dense PK Substudy were taken prior to blood sample collection using AOBP measurement with the Omron Model HEM 907XL (or comparable). Measures were recorded in the eCRF. Detailed instructions could be found in the study manual.

b Additional blood pressure assessment between screening and baseline, to confirm eligibility for participants in the Dense PK Substudy. Screening 2 could occur on the same day as the screening visit.

c On Day 1, the 4 hour and 8 hour PK sampling was to be within ±30 minutes and ±2 hours, respectively, of the scheduled time. For subsequent days, PK sampling was to be performed within ±2 hours of the clock time of dosing on Day 1.

Source: Table 7-4 of Study PULSAR CSR

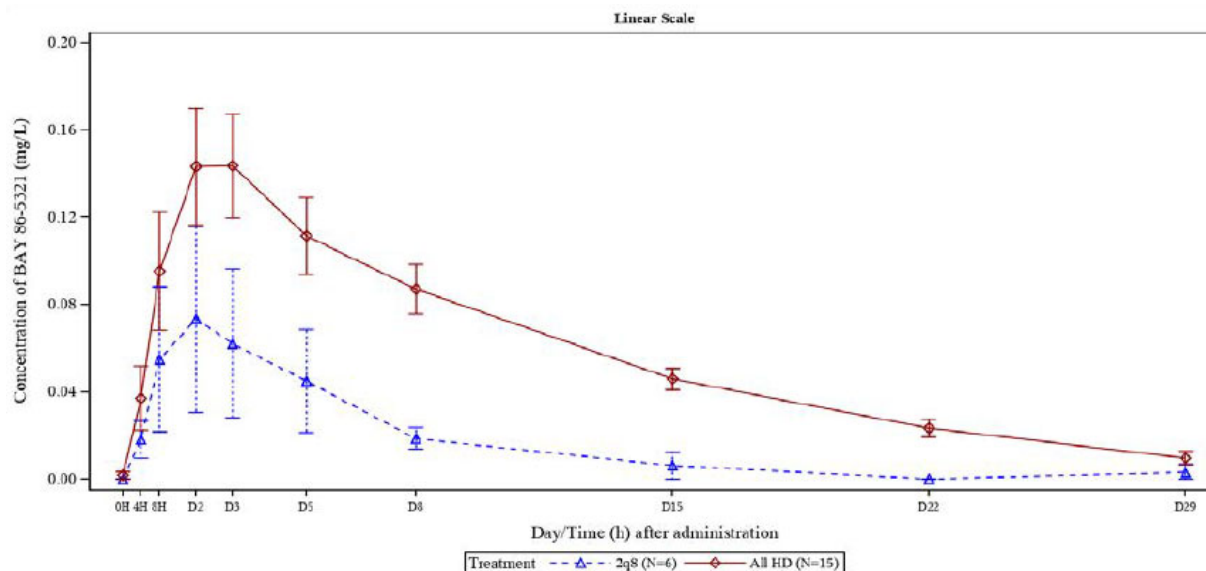
Immunogenicity sampling: baseline, Week 48

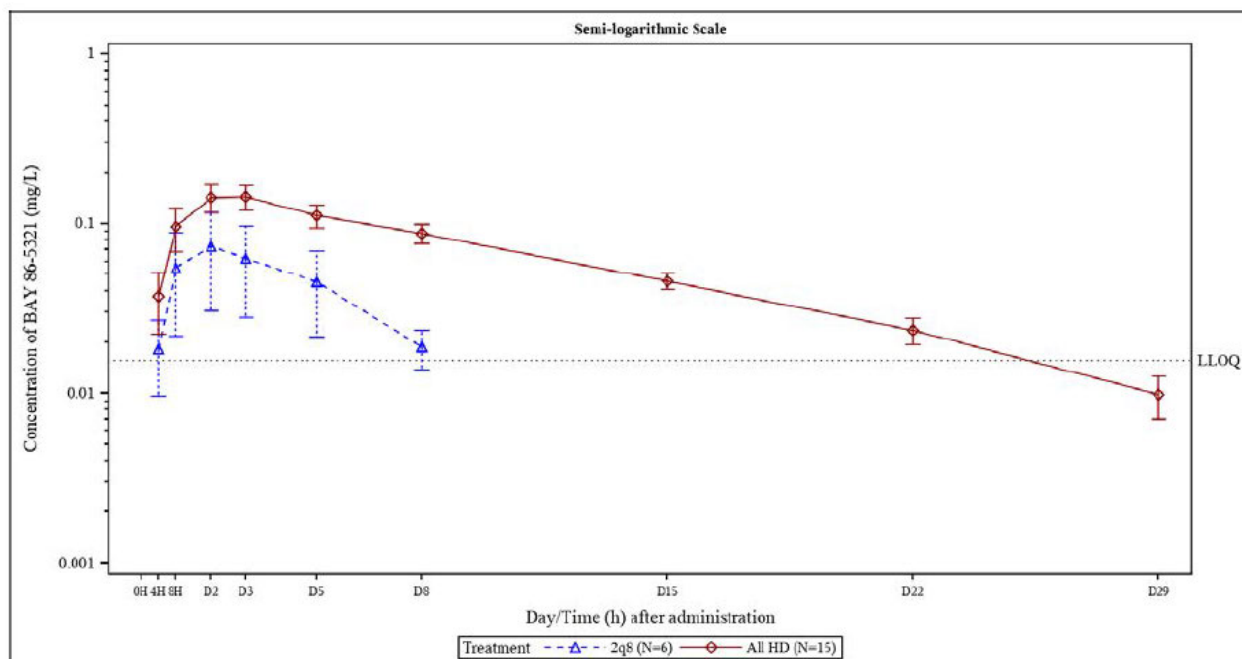
PK Results

The PK profiles and PK parameters of free, adjusted, and total aflibercept in plasma are shown as below.

Free aflibercept in dense PK substudy

Figure 19. Arithmetic mean/SD concentrations of free aflibercept in plasma by nominal time and treatment in participants with unilateral treatment in the dense PK sampling substudy up to Day 29 (Study PULSAR, linear and semi-log scale)





DPKS = dense pharmacokinetic analysis set, LLOQ = Lower level of quantification, N = Number of participants with unilateral treatment up to Week 48, PK = pharmacokinetic, SD = Standard deviation
 2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
 All HD: Pooled high dose aflibercept 8 mg administered every 12 weeks or every 16 weeks, after 3 initial injections at 4-week intervals.

Source: Figure 9-5 of Study PULSAR CSR

Table 21. Summary statistics of free aflibercept PK parameters in plasma in participant with unilateral treatment from pooled region: Rest of the World – Dense PK substudy (Study PULSAR)

Pooled region	PK parameter (unit)	Treatment	n	Geom. mean (SD)	Geom. Mean 95% CI	Geom. CV (%)	Arithm. mean (SD)	Arithm. CV (%)	Median	Min, Max
Rest of the World	Cmax (mg/L)	2q8 (N = 6)	6	0.0469 (2.51)	0.02, 0.12	116	0.0758 (0.103)	136	0.0357	0.0223, 0.286
		HDq12+HDq16 (N = 11)	11	0.115 (1.95)	0.06, 0.22	74.8	0.137 (0.0755)	55.0	0.111	0.0288, 0.231
	Cmax/Dose (mg/L/mg)	2q8 (N = 6)	6	0.0235 (2.51)	0.01, 0.06	116	0.0379 (0.0517)	136	0.0179	0.0112, 0.143
		HDq12+HDq16 (N = 11)	11	0.0144 (1.95)	0.01, 0.03	74.8	0.0171 (0.00943)	55.0	0.0139	0.0036, 0.0289
	Clast (mg/L)	2q8 (N = 6)	6	0.0202 (1.12)	0.02, 0.02	11.5	0.0203 (0.00226)	11.1	0.0202	0.0165, 0.0235
		HDq12+HDq16 (N = 11)	11	0.0217 (1.44)	0.02, 0.03	37.6	0.0233 (0.0113)	48.7	0.0183	0.0164, 0.0549
	Ctrough (mg/L) Day 29	2q8 (N = 6)	5	0.0165 (NE)	NE	NE	0.00330 (0.00738)	224	0.00	0.00, 0.0165
		HDq12+HDq16 (N = 11)	10	0.0186 (1.14)	0.02, 0.02	13.3	0.00750 (0.00980)	131	0.00	0.00, 0.0226
	AUClast (day*mg/L)	2q8 (N = 6)	6	0.188 (3.17)	0.06, 0.60	167	0.362 (0.538)	149	0.18	0.0532, 1.45
		HDq12+HDq16 (N = 11)	11	1.12 (1.99)	0.56, 2.23	78.0	1.28 (0.476)	37.1	1.31	0.156, 1.85
	AUCinf (day*mg/L)	2q8 (N = 6)	0							
		HDq12+HDq16 (N = 11)	7	1.73 (1.19)	1.46, 2.05	17.2	1.749 (0.26879)	15.4	1.83	1.22, 1.98
	AUCinf/Dose (day*mg/L/mg)	2q8 (N = 6)	0							
		HDq12+HDq16 (N = 11)	7	0.216 (1.19)	0.18, 0.26	17.2	0.219 (0.0336)	15.4	0.229	0.153, 1.98
	AUC(0-28d) Norm by WT (day*mg/L/kg)	2q8 (N = 6)	3	0.0059 (2.26)	0.00, 0.01	96.9	0.00753 (0.00656)	87.1	0.00413	0.0034, 0.0151
		HDq12+HDq16 (N = 11)	9	0.0172 (1.32)	0.01, 0.02	27.9	0.0177 (0.00441)	24.9	0.0161	0.0098, 0.0232
	Accumulation Ratio (C _{Week12} /C _{Week4})	2q8 (N = 6)	1	NE (NE)	NE	NE	0.00 (NE)	NE	0.00	0.00, 0.00
		HDq12+HDq16 (N = 11)	4	1.16 (1.11)	1.05, 1.29	10.2	1.165 (0.118)	10.1	1.17	1.04, 1.28
	t _{1/2} (day)	2q8 (N = 6)	2	5.93 (1.04)	5.72, 6.16	3.71	5.94 (0.220)	3.71	5.94	5.78, 6.09
		HDq12+HDq16 (N = 11)	9	10.3 (1.95)	5.30, 20.1	74.7	13.3 (13.1)	98.6	10.6	5.21, 47.3
	t _{max} (day)	2q8 (N = 6)	6						1.05	0.333, 1.95
		HDq12+HDq16 (N = 11)	11						1.93	0.333, 4.03
	t _{last} (day)	2q8 (N = 6)	6						6.98	2.00, 26.9
		HDq12+HDq16 (N = 11)	11						21.1	7.05, 28.1

Arithm. = arithmetic, AUCinf = Area under the curve from time zero to infinity, AUClast = Area under the curve to the last quantifiable concentration, CI = confidence interval, Clast = Last concentration, Cmax = Maximum concentration, Ctrough = trough concentration, CV = coefficient of variation, geom. = geometric, DPKS = dense pharmacokinetic analysis set, LLOQ = Lower level of quantification, Max = Maximum, Min = Minimum, N = Number of participants with unilateral treatment up to Week 48, n = Number of observations, NE = Not Evaluable, PK = pharmacokinetic, SD = Standard deviation, t_{1/2} = half-life, t_{last} = time to last concentration, t_{max} = time to maximum concentration, WT = weight.

For Clast, values below LLOQ were substituted by 1/2 LLOQ for the calculation of geometric statistics and 0 for arithmetic statistics.

See Definition of terms for treatment group description.

Source: Table 14.4/28.1 (post-hoc) and Table 14.4/31.1 (post-hoc)

Source: Table 9-21 of Study PULSAR CSR

Table 22. Summary statistics of free aflibercept PK parameters in plasma in participants with unilateral treatment from pooled region: Japan – Dense PK substudy (Study PULSAR)

Pooled region	PK parameter (unit)	Treatment	n	Geom. mean (SD)	Geom. Mean 95% CI	Geom. CV (%)	Arithm. mean (SD)	Arthm. CV (%)	Median	Min, Max
Japan	Cmax (mg/L)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	1	0.393 (NE)	NE	NE	0.393 (NE)	NE	0.39300	0.393, 0.393
	Cmax/Dose (mg/L/mg)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	1	0.0491 (NE)	NE	NE	0.0491 (NE)	NE	0.0491	0.0491, 0.0491
	Clast (mg/L)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	1	0.0169 (NE)	NE	NE	0.0169 (NE)	NE	0.01690	0.0169, 0.0169
	Ctrough (mg/L)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	1	0.0169 (NE)	NE	NE	0.0169 (NE)	NE	0.01690	0.0169, 0.0169
	AUClast (day*mg/L)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	1	3.51 (NE)	NE	NE	3.51 (NE)	NE	3.51	3.51, 3.51
	AUCinf (day*mg/L)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	1	3.66 (NE)	NE	NE	3.66 (NE)	NE	3.66	3.66, 3.66
	AUCinf/Dose (day*mg/L/mg)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	1	0.457 (NE)	NE	NE	0.457 (NE)	NE	0.457	0.457, 0.457
	AUC(0-28d) Norm by WT (day*mg/L/kg)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	1	0.0807 (NE)	NE	NE	0.0807 (NE)	NE	0.0807	0.0807, 0.0807
	Accumulation Ratio (CWeek12/CWeek4)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	1	1.37 (NE)	NE	NE	1.37 (NE)	NE	1.37	1.37, 1.37
	t1/2 (day)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	1	6.03 (NE)	NE	NE	6.03 (NE)	NE	6.03	6.03, 6.03
	tmax (day)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 1)	1						1.02	1.02, 1.02
	tlast (day)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 1)	1						27.9	27.9, 27.9

Arithm. = arithmetic, AUCinf = Area under the curve from time zero to infinity, AUClast = Area under the curve to the last quantifiable concentration, CI = confidence interval, Clast = Last concentration, Cmax = Maximum concentration, Ctrough = trough concentration, CV = coefficient of variation, geom. = geometric, DPKS = dense pharmacokinetic analysis set, geom. = geometric, LLOQ = Lower level of quantification, Max = Maximum, Min = Minimum, N = Number of participants with unilateral treatment up to Week 48, n = Number of observations, NE = Not Evaluable, PK = pharmacokinetic, SD = Standard deviation, t1/2 = half-life, tlast = time to last concentration, tmax = time to maximum concentration, WT = weight. For Clast, values below LLOQ were substituted by 1/2 LLOQ for the calculation of geometric statistics and 0 for arithmetic statistics.

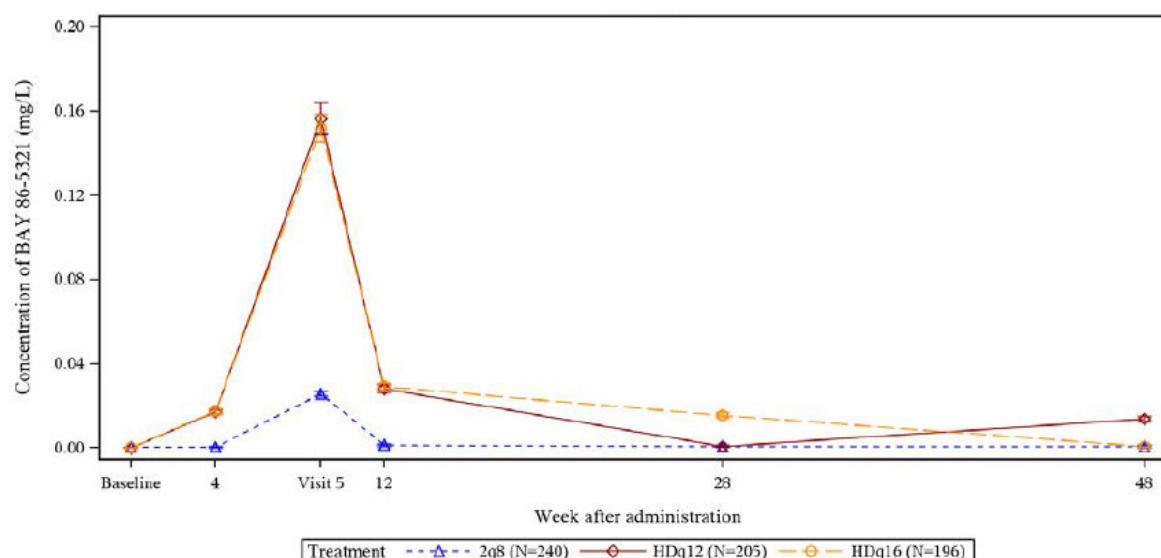
See Definition of terms for treatment group description.

Source: [Table 14.4/28.1](#) (post-hoc) and [Table 14.4/31.1](#) (post-hoc)

Source: Table 9-22 of Study PULSAR CSR

Free aflibercept in all participants

Figure 20. Arithmetic mean/SD concentrations of free aflibercept in plasma by nominal time and treatment in participants with unilateral treatment and without DRMs up to Week 48 (Study PULSAR, linear scale)



Source: Figure 9-7 of Study PULSAR CSR

Table 23. Summary of concentration of free aflibercept (mg/L) in plasma by time and treatment in participants with unilateral treatment and without DRMs up to Week 48 (Study PULSAR)

Time	Treatment	n total	n ≥ LLOQ	Free aflibercept	
				Geom. Mean ± SD	Arithm. Mean ± SD
Baseline (Visit 2)	2q8 (N = 240)	230	3	N.C	0.00032 (0.00302)
	HDq12 (N = 205)	191	0	N.C	0.00 (0.00)
	HDq16 (N = 196)	181	0	N.C	0.00 (0.00)
Week 4 (Visit 3)	2q8 (N = 240)	222	4	N.C	0.00044 (0.00369)
	HDq12 (N = 205)	194	122	N.C	0.0172 (0.0157)
	HDq16 (N = 196)	184	119	N.C	0.0174 (0.0166)
Visit 5	2q8 (N = 240)	203	169	0.02 (1.81)	0.0257 (0.0163)
	HDq12 (N = 205)	178	175	0.13 (1.97)	0.157 (0.101)
	HDq16 (N = 196)	165	161	0.13 (2.03)	0.152 (0.0825)
Week 12 (Visit 6)	2q8 (N = 240)	219	11	N.C	0.00134 (0.00657)
	HDq12 (N = 205)	192	155	0.02 (1.99)	0.0282 (0.0227)
	HDq16 (N = 196)	188	149	0.02 (2.02)	0.0293 (0.0225)
Week 28 (Visit 10)	2q8 (N = 240)	198	4	N.C	0.00069 (0.00609)
	HDq12 (N = 205)	185	6	N.C	0.00089 (0.00528)
	HDq16 (N = 196)	177	101	N.C	0.0156 (0.0164)
Week 48 (Visit 15)	2q8 (N = 240)	195	1	N.C	0.00070 (0.00981)
	HDq12 (N = 205)	176	86	N.C	0.0137 (0.0179)
	HDq16 (N = 196)	159	4	N.C	0.00059 (0.00382)

Arithm. = arithmetic, DRM = dose regimen modification, geom. = geometric, LLOQ = Lower level of quantification, N = Number of participants with unilateral treatment and without DRMs up to Week 48, n = Number of observations, PKS = pharmacokinetic analysis set, SD = Standard deviation

N.C.: not calculated (less than 2/3 of values per timepoint are ≥ LLOQ for geometric mean calculation).

Values below LLOQ (0.0156 mg/L) were substituted by 1/2 LLOQ for the calculation of geometric statistics and 0 for arithmetic statistics and median.

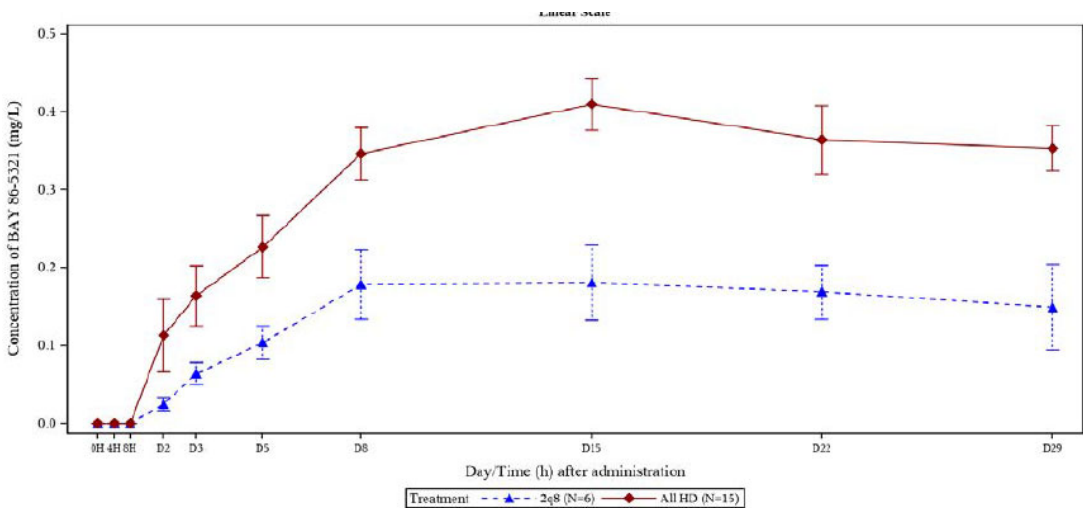
See Definition of terms for treatment group description.

Source: Table 14.4/1.1 (post-hoc)

Source: Table 9-27 of Study PULSAR CSR

Adjusted bound aflibercept in dense PK substudy

Figure 21. Arithmetic mean/sd concentrations of adjusted bound aflibercept in plasma by nominal time and treatment in participants with nAMD with unilateral treatment in the dense PK sampling substudy up to Day 29 (Study PULSAR, linear scale)



Source: Figure 9-6 of Study PULSAR CSR

Table 24. Summary statistics of adjusted bound aflibercept PK parameters in plasma in participants with unilateral treatment for pooled region: Rest of the World – Dense PK substudy (Study PULSAR)

Pooled region	PK parameter (unit)	Treatment	n	Geom. mean (SD)	Geom. Mean 95% CI	Geom. CV (%)	Arithm. mean (SD)	Arthm. CV (%)	Median	Min, Max
Rest of the World	Cmax (mg/L)	2q8 (N = 6)	6	0.164 (1.54)	0.11, 0.25	44.9	0.179 (0.0950)	53.0	0.158	0.108, 0.368
		HDq12+HDq16 (N = 11)	11	0.415 (1.50)	0.28, 0.62	42.6	0.441 (0.138)	31.3	0.424	0.143, 0.611
	Cmax/Dose (mg/L/mg)	2q8 (N = 6)	6	0.0821 (1.54)	0.05, 0.13	44.9	0.0897 (0.0475)	53.0	0.0789	0.0541, 0.184
		HDq12+HDq16 (N = 11)	11	0.0519 (1.50)	0.03, 0.08	42.6	0.0552 (0.0173)	31.3	0.0531	0.0178, 0.0764
	Clast (mg/L)	2q8 (N = 6)	6	0.120 (1.78)	0.07, 0.21	63.1	0.142 (0.112)	78.5	0.106	0.0739, 0.368
		HDq12+HDq16 (N = 11)	11	0.325 (1.40)	0.23, 0.46	34.8	0.341 (0.0966)	28.4	0.338	0.143, 0.512
	Ctrough (mg/L) Day 29	2q8 (N = 6)	5	0.122 (1.90)	0.06, 0.23	71.8	0.149 (0.124)	82.7	0.105	0.0739, 0.368
		HDq12+HDq16 (N = 11)	10	0.317 (1.41)	0.22, 0.45	35.4	0.332 (0.0970)	29.3	0.336	0.143, 0.512
	AUClast (day*mg/L)	2q8 (N = 6)	6	3.42 (1.66)	2.06, 5.68	54.2	3.84 (2.21)	57.6	3.34	1.77, 8.08
		HDq12+HDq16 (N = 11)	11	7.98 (1.47)	5.43, 11.7	39.8	8.45 (2.64)	31.3	8.00	3.12, 12.3
	AUCinf (day*mg/L)	2q8 (N = 6)	0							
		HDq12+HDq16 (N = 11)	0							
	AUCinf/Dose (day*mg/L/mg)	2q8 (N = 6)	0							
		HDq12+HDq16 (N = 11)	0							
	AUC(0-28d) Norm by WT (day*mg/L/kg)	2q8 (N = 6)	2	0.0379 (1.19)	0.03, 0.05	17.9	0.0382 (0.00673)	17.6	0.0382	0.0334, 0.0429
		HDq12+HDq16 (N = 11)	5	0.118 (1.55)	0.08, 0.18	46.2	0.127 (0.0514)	40.3	0.140	0.069, 0.190
	Accumulation Ratio (C _{Week12} /C _{Week4})	2q8 (N = 6)	5	1.68 (1.63)	1.04, 2.74	51.6	1.83 (0.766)	41.8	1.66	0.790, 2.75
		HDq12+HDq16 (N = 11)	10	1.59 (1.53)	1.04, 2.42	44.2	1.72 (0.774)	45.0	1.58	0.707, 3.55
	t _{1/2} (day)	2q8 (N = 6)	1	25.3 (NE)	NE	NE	25.3 (NE)	NE	25.3	25.3, 25.3
		HDq12+HDq16 (N = 11)	1	281 (NE)	NE	NE	281 (NE)	NE	281	281, 281
	t _{max} (day)	2q8 (N = 6)	6						14.0	7.05, 21.0
		HDq12+HDq16 (N = 11)	11						14.1	1.03, 28.1
	t _{last} (day)	2q8 (N = 6)	6						28.0	21.0, 29.2
		HDq12+HDq16 (N = 11)	11						27.9	21.0, 32.0

Arithm. = arithmetic, AUCinf = Area under the curve from time zero to infinity, AUClast = Area under the curve to the last quantifiable concentration, CI = confidence interval, Clast = Last concentration, Cmax = Maximum concentration, Ctough = trough concentration, CV = coefficient of variation, geom. = geometric, DPKS = dense pharmacokinetic analysis set, LLOQ = Lower level of quantification, Max = Maximum, Min = Minimum, N = Number of participants with unilateral treatment up to Week 48, n = Number of observations, NE = Not Evaluable, PK = pharmacokinetic, SD = Standard deviation, t_{1/2} = half-life, t_{last} = time to last concentration, t_{max} = time to maximum concentration, WT = weight.

For Clast, values below LLOQ were substituted by 1/2 LLOQ for the calculation of geometric statistics and 0 for arithmetic statistics.

See Definition of terms for treatment group description.

Source: Table 14.4/29.1 (post-hoc) and Table 14.4/32.1 (post-hoc)

Source: Table 9-24 of Study PULSAR CSR

Table 25. Summary statistics of adjusted bound aflibercept PK parameters in plasma in participants with unilateral treatment for pooled region: Japan – dense PK substudy (Study PULSAR)

Pooled region	PK parameter (unit)	Treatment	n	Geom. mean (SD)	Geom. Mean 95% CI	Geom. CV (%)	Arithm. mean (SD)	Arthm. CV (%)	Median	Min, Max
Japan	Cmax (mg/L)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	1	0.567 (NE)	NE	NE	0.567 (NE)	NE	0.567	0.567, 0.567
	Cmax/Dose (mg/L/mg)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	1	0.0709 (NE)	NE	NE	0.0709 (NE)	NE	0.0709	0.0709, 0.0709
	Clast (mg/L)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	1	0.412 (NE)	NE	NE	0.412 (NE)	NE	0.412	0.412, 0.412
	Ctrough (mg/L) Day 29	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	1	0.412 (NE)	NE	NE	0.412 (NE)	NE	0.412	0.412, 0.412
	AUClast (day*mg/L)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	1	11.7 (NE)	NE	NE	11.7 (NE)	NE	11.7	11.7, 11.7
	AUCinf (day*mg/L)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	0							
	AUCinf/Dose (day*mg/L/mg)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	0							
	AUC(0-28d) Norm by WT (day*mg/L/kg)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	0							
	Accumulation Ratio (C _{Week12} /C _{Week4})	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	1	1.47 (NE)	NE	NE	1.47 (NE)	NE	1.47	1.47, 1.47
	t _{1/2} (day)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	0							
	t _{max} (day)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	1						14.0	14.0, 14.0
	t _{last} (day)	2q8 (N = 0)	0							
		HDq12+HDq16 (N = 2)	1						27.9	27.9, 27.9

Arithm. = arithmetic, AUCinf = Area under the curve from time zero to infinity, AUClast = Area under the curve to the last quantifiable concentration, CI = confidence interval, Clast = Last concentration, Cmax = Maximum concentration, Ctrough = trough concentration, CV = coefficient of variation, geom. = geometric, DPKS = dense pharmacokinetic analysis set, LLOQ = Lower level of quantification, Max = Maximum, Min = Minimum, N = Number of participants with unilateral treatment up to Week 48, n = Number of observations, NE = Not Evaluable, PK = pharmacokinetic, SD = Standard deviation, t_{1/2} = half-life, t_{last} = time to last concentration, t_{max} = time to maximum concentration, WT = weight.

For Clast, values below LLOQ were substituted by 1/2 LLOQ for the calculation of geometric statistics and 0 for arithmetic statistics.

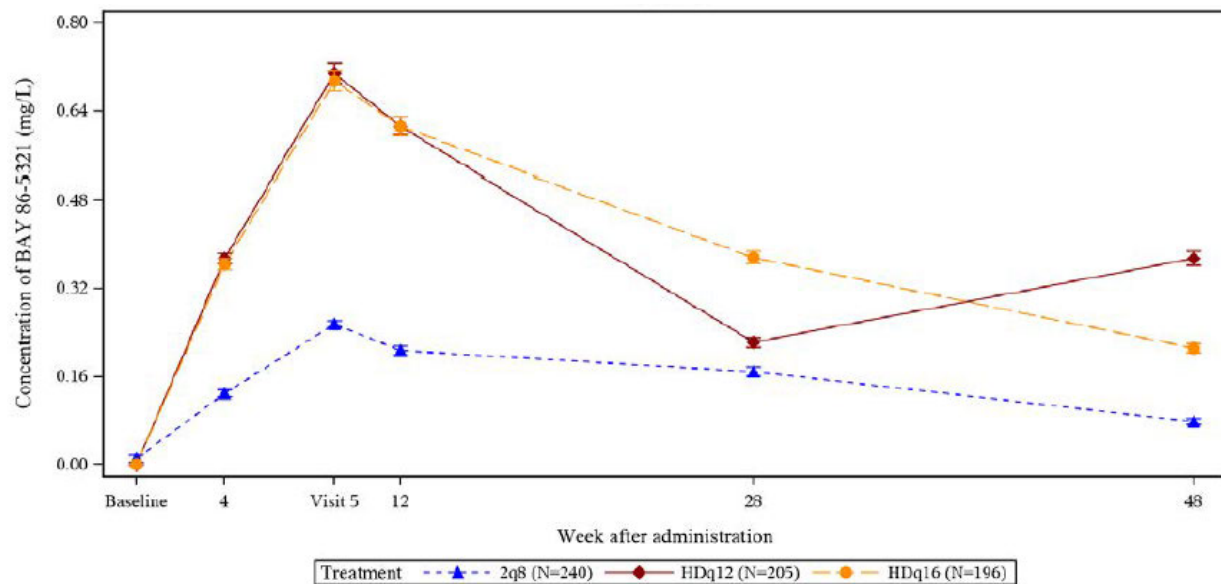
See Definition of terms for treatment group description.

Source: [Table 14.4/29.1](#) (post-hoc) and [Table 14.4/32.1](#) (post-hoc)

Source: Table 9-25 of Study PULSAR CSR

Adjusted bound aflibercept in all participants

Figure 22. Arithmetic mean/SD concentrations of adjusted bound aflibercept in plasma by nominal time and treatment in participants with unilateral treatment and without DRMs up to Week 48 (Study PULSAR, linear scale)



Source: Figure 9-8 of Study PULSAR CSR

Table 26. Summary of concentration of adjusted bound aflibercept (mg/L) in plasma by time and treatment in participants with unilateral treatment and without DRMs up to Week 48 (Study PULSAR)

Time	Treatment	n total	Adjusted bound aflibercept		
			n ≥ LLOQ	Geom. Mean ± SD	Arithm. Mean ± SD
Baseline (Visit 2)	2q8 (N = 240)	230	7	N.C	0.0108 (0.0911)
	HDq12 (N = 205)	191	1	N.C	0.00029 (0.00402)
	HDq16 (N = 196)	181	2	N.C	0.00079 (0.00915)
Week 4 (Visit 3)	2q8 (N = 240)	222	218	0.11 (1.67)	0.130 (0.0836)
	HDq12 (N = 205)	194	193	0.34 (1.64)	0.375 (0.132)
	HDq16 (N = 196)	184	183	0.33 (1.72)	0.364 (0.143)
Visit 5	2q8 (N = 240)	203	201	0.24 (1.59)	0.255 (0.0924)
	HDq12 (N = 205)	178	176	0.64 (1.76)	0.708 (0.248)
	HDq16 (N = 196)	165	164	0.64 (1.64)	0.694 (0.229)
Week 12 (Visit 6)	2q8 (N = 240)	219	217	0.18 (1.72)	0.207 (0.120)
	HDq12 (N = 205)	192	192	0.57 (1.46)	0.613 (0.216)
	HDq16 (N = 196)	188	187	0.56 (1.64)	0.612 (0.223)
Week 28 (Visit 10)	2q8 (N = 240)	198	197	0.15 (1.61)	0.169 (0.109)
	HDq12 (N = 205)	185	183	0.19 (1.83)	0.222 (0.120)
	HDq16 (N = 196)	177	172	0.33 (2.06)	0.377 (0.149)
Week 48 (Visit 15)	2q8 (N = 240)	195	180	0.06 (2.05)	0.0787 (0.0706)
	HDq12 (N = 205)	176	168	0.30 (2.38)	0.375 (0.177)
	HDq16 (N = 196)	159	157	0.18 (1.86)	0.211 (0.109)

Arithm. = arithmetic, DRM = dose regimen modification, geom. = geometric, LLOQ = Lower level of quantification, N = Number of participants with unilateral treatment and without DRMs up to Week 48, n = Number of observations, PKS = pharmacokinetic analysis set, SD = Standard deviation

N.C.: not calculated (less than 2/3 of values per timepoint are ≥ LLOQ for geometric mean calculation).

Values below LLOQ (0.022442 mg/L) were substituted by 1/2 LLOQ for the calculation of geometric statistics and 0 for arithmetic statistics and median.

See Definition of terms for treatment group description.

Source: [Table 14.4/10.1](#) (post-hoc)

Source: Table 9-28 of Study PULSAR CSR

Immunogenicity Assessment

Out of the 793 participants, a total of 42 participants had positive samples in the ADA assay (including baseline): 11 participants in the 2q8 group, 18 participants in the HDq12 group, and 13 participants in the HDq16 group. A total of 24 participants participating in this study exhibited a treatment-emergent ADA response: 4 participants in the 2q8 group, 11 participants in the HDq12 group, and 9 participants in the HDq16 group. The incidence of treatment-emergent immunogenicity in the 2q8, HDq12 and HDq16 groups was approximately 1.5%, 4.1%, and 3.4%, respectively. In each of the groups, the titers were low (<1000). None of the samples that were positive in the ADA assay demonstrated neutralizing activity.

Table 27. Number of participants with anti-drug antibodies to aflibercept at Week 48 (Study PULSAR)

Visit	Category	2q8 N = 260 (100%)	HDq12 N = 269 (100%)	HDq16 N = 264 (100%)	All HD N = 533 (100%)
Week 48	Total ADA subjects, n (%)	260 (100%)	269 (100%)	264 (100%)	533 (100%)
	Negative (a)	249 (95.8%)	250 (92.9%)	250 (94.7%)	500 (93.8%)
	Pre-existing immunoreactivity (b)	7 (2.7%)	7 (2.6%)	4 (1.5%)	11 (2.1%)
	Treatment-boosted (c)	0	0	0	0
	Treatment-emergent positive (d)	4 (1.5%)	11 (4.1%)	9 (3.4%)	20 (3.8%)
	Missing	0	1 (0.4%)	1 (0.4%)	2 (0.4%)
	Titer				
	Low (< 1000)	4	11	9	20
	Moderate (1000-10000)	0	0	0	0
	High (> 10000)	0	0	0	0
	Number of subjects treatment-emergent NAb ADA positive	0	0	0	0

ADA = anti-drug antibody, NAb = neutralizing antibody

(a) ADA Negative: negative response in the ADA assay at all time points and those that exhibited a pre-existing response, as defined in (b), regardless of any missing samples.

(b) Pre-existing immunoreactivity: either a positive response in the ADA assay at baseline with all post first dose ADA results negative OR a positive response at baseline with all post first dose ADA responses less than 4-fold of baseline titer levels.

(c) Treatment-boosted ADA response: positive response post first dose that is greater than or equal to 4-fold over baseline titer level, when baseline results were positive.

(d) Treatment-emergent positive: ADA positive response post first dose when baseline results were negative or missing.

See Definition of terms for treatment group description.

Source: [Table 14.3.7/22](#), [Table 14.3.7/23](#), and [Table 14.3.7/24](#)

Source: Table 9-29 of Study PULSAR CSR

4.3 Pharmacometrics Review

1. Population PK analysis

1.1 Review Summary

The applicant's population pharmacokinetics (PopPK) analysis of free and adjusted bound aflibercept, intravitreally administered anti-vascular endothelial growth factor therapies to inhibit neovascular vessel growth and leakage in the retina, is acceptable to support the current submission as outlined in Table 28. The applicant's final PopPK model adequately described the free and adjusted bound aflibercept concentrations, in which PopPK parameter estimates were estimated with acceptable precision as indicated by the relative standard errors. The goodness-of-fit plots showed a good agreement between the observed and the individual predicted concentrations without any obvious bias over time or predicted concentrations. The prediction-corrected visual predictive check plots showed a good agreement between the observed and the simulated concentrations. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

There were no clinically meaningful differences found in the exposure metrics of aflibercept between age categories, albumin categories, hepatic function categories, renal impairment categories, Asian and non-Asian, or Japanese and non-Japanese participants. Therefore, there is no dose adjustment requirement for renal patients and mild hepatic patients.

Table 28. Specific Comments on Applicant's Final Population PK model

Utility of the final model			Reviewer's Comments
Support applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	Based on a PopPK analysis, renal impairment, and mild hepatic impairment, do not have a clinically meaningful effect on the PK. Dose adjustment based on renal impairment and mild hepatic impairment is not required. Body weight, age, albumin, and high dose (HD 8 mg) were identified as statistically significant covariates	The applicant's recommendation that there is no dose adjustment for renal patients and mild hepatic patients is acceptable.
	Extrinsic factor	NA	NA
Derive exposure metrics for Exposure-response analyses	Cmin		The applicant's final model is generally acceptable for generating exposure metrics for exposure-response analyses (Table 32).

1.2 Introduction

The primary objectives of applicant's analysis were to:

- Develop a population PK (PopPK) model to characterize concentration-time profiles of free and adjusted bound aflibercept in plasma
- Estimate population and individual PK parameters of aflibercept in patients with neovascular age-related macular (nAMD) and diabetic macular edema (DME)
- Investigate the effects of relevant covariates which may explain variability in aflibercept PK parameters
- Derive post hoc estimates from the final PopPK model to predict individual exposure metrics in nAMD and DME patients that also form a basis for pharmacokinetic/pharmacodynamic (PK/PD) analyses

1.3 PopPK Model development

Data

The PopPK analysis included free and adjusted bound aflibercept concentration-time data from 13 clinical studies in patients with nAMD or DME receiving aflibercept as intravenous (IV) or intravitreal (IVT) injections, 2 studies in healthy male subjects receiving either subcutaneous (SC) or IV doses, and 1 study in patients with solid tumors or lymphoma receiving SC doses of aflibercept. The addition of the SC oncology study provided information at a lower dose range similar to those observed following IVT dosing. Pertinent details regarding the design and sampling schedules are summarized shown in Table 29.

Concentration data which were below the limit of quantitation (BLQ) were included and flagged in the analysis dataset. There were 9785 (62.8%) of the 15571 free aflibercept concentrations, and 3070 (19.7%) of the 15583 adjusted bound concentrations that were BLQ. Due to the large percentage of post-dose BLQ records in the data, the M3 method was applied.

Data can be classified as outliers using the population conditional weighted residuals (CWRES). Prior to covariate analysis, observations with $|CWRES| > 5$ are considered potential outliers and are excluded from subsequent model development. However, a sensitivity analysis will be performed where the proposed final model will be re-run with these outliers re-included in the analysis.

If the patient received a dose, and the dosing date or dosing time for subsequent doses are not recorded or missing, dosing date or time may be imputed based on planned dosing date and/or time per protocol. If sampling date or time is not recorded or is missing, it may be imputed using planned time per protocol relative to the dose. Relevant documents such as protocols, bioanalytical reports, and clinical study reports may be utilized to provide information for imputation of missing date/time of dose or PK sampling.

Table 29. Summary of Clinical Study Designs

Study Number/Phase	Study Title	Study Population	Dosing Regimens	Pharmacokinetic Sampling Schedule
PDY6655 / Phase 1	A Phase I, Single-center, Randomized, Open-label, Single-dose, Crossover Study to Compare the Cardiovascular Pharmacodynamics and Pharmacokinetics of Subcutaneous versus Intravenous VEGF Trap in Healthy Male Subjects	Healthy male subjects	2 mg/kg IV SD and SC SD (N=20) 2 mg/kg SC SD and IV SD (N=20)	Predose, Days 1, 2, 3, 5, 7, 15, 29, and 43
PDY6656 / Phase 1	A Phase I, Single-center, Randomized, Double-blind, Placebo-controlled, Sequential Ascending Dose Study to Assess the Cardiovascular Pharmacodynamics and the Pharmacokinetics of Single IV Infusion of VEGF Trap in Healthy Male Subjects	Healthy male subjects	1 mg/kg IV SD (N=12) 2 mg/kg IV SD (N=12) 4 mg/kg IV SD (N=12)	Predose, 1, 2, 4, 6, 8, 12 hr post-dose on Days 1, 2, 3, 8, 15, 22, 29, 36, and 43
TED6113 / Phase 1 (VGFT-ST-0103)	An Open Label, Sequential Cohort, Dose-Escalation Safety, Tolerability, and Pharmacokinetic Study of AVE0005 (VEGF Trap) in Subjects with Incurable, Relapsed, or Refractory Solid Tumors or Lymphoma	Patients with solid tumors or lymphoma	Single SC doses of 25 µg/kg (N=3), 50 µg/kg (N=4), 100 µg/kg (N=6), 200 µg/kg (N=4), 400 µg/kg (N=6), 800 µg/kg (N=7) and 800 µg/kg 2x weekly (N=8), all followed by 6 weekly SC injections at the same dose level starting 4 weeks after the first dose	Predose, 1, 2, 4, 8, 24, 30, 48, 72, 120, and 168 hours post-dose and on Days 15, 22, 29, 36, 43, 50, 57, 64, 71, and 92. 800 µg/kg twice weekly dose level cohort had additional blood sampling on Days 11 and 32

Study Number/Phase	Study Title	Study Population	Dosing Regimens	Pharmacokinetic Sampling Schedule
VGFT-OD-0305 / Phase 1	An Exploratory Study of the Safety, Tolerability and Biological Activity of Intravenously Administered VEGF Trap in Patients with Neovascular Age-Related Macular Degeneration	nAMD Patients	0.3 mg/kg IV (Q2W 4 weeks after 1st dose) (N=7) 1 mg/kg IV Q2W 4 weeks after 1st dose (N=7) 3 mg/kg IV Q2W 4 weeks after 1st dose (N=5)	Screening, pre-dose, 2h, 4h, Days 2, 4, 8, 15, 22, 29, 36, 43, 57, 71, 85, and 99, followed by 3 times at 12-week intervals beginning after the last dose of study drug
VGFT-OD-0306 / Phase 1	An Open Label, Long-Term, Safety and Tolerability Study of VEGF Trap Administered Intravenously in Patients with Neovascular Age-Related Macular Degeneration	nAMD Patients	0.3 mg/kg IV Q2W (N=4) 1 mg/kg IV Q2W (N=3) These 7 patients were from Study VGFT-OD-0305 and enrolled into Study VGFT-OD-0306.	Weeks 2, 4, 6, 10, 14, and 18 (plasma samples were taken prior to start of each drug infusion)
VGFT-OD-0307 / Phase 1	An Exploratory Study of the Safety, Tolerability and Biological Activity of Intravenously Administered VEGF Trap in Patients with Diabetic Macular Edema	DME Patients	0.3 mg/kg IV Q2W (N=6)	Plasma samples were obtained at screening, pre-dose, Days 8, 15, 29, 43, 57, 71, 85, and 133 (3 months after the last infusion).

Study Number/Phase	Study Title	Study Population	Dosing Regimens	Pharmacokinetic Sampling Schedule
VGFT-OD-0502 (Part A) / Phase 1	An Exploratory Study of the Safety, Tolerability, and Biological Effect of Intravitreal Administration of VEGF Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration: Part A of the Study	nAMD Patients	0.05 mg IVT SD (N=3) 0.15 mg IVT SD (N=3) 0.5 mg IVT SD (N=3) 1 mg IVT SD (N=6) 2 mg IVT SD (N=3) 4 mg IVT SD (N=2) Note: Fellow eye treatment was allowed during the study	Pre-dose and every 3 months thereafter.
VGFT-OD-0502 (Part C)/ Phase 1	An Exploratory Study of the Safety, Tolerability, and Biological Effect of Intravitreal Administration of VEGF Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration: Part C of the Study	nAMD Patients	0.15 mg IVT Q8W (N=14) 4 mg IVT Q8W (N=14) Note: Fellow eye treatment was allowed during the study	Pre-dose, Days 3, 8, 15, 29, 43, 57, and 85 Optional open-label visits (OL-D1, Months 3, 6, 9, and 12)
VGFT-OD-0512 (CLEAR-IT DME 1) / Phase 1	An Exploratory Study of the Safety, Tolerability, and Biological Effect of a Single Intravitreal Administration of VEGF Trap-Eye in Patients with Diabetic Macular Edema	DME Patients	4 mg IVT SD (N=5)	Screening, pre-dose, Days 3, 8, 15, 29, 43, and 155

Study Number/Phase	Study Title	Study Population	Dosing Regimens	Pharmacokinetic Sampling Schedule
VGFT-OD-0603 (CLEAR-IT 1b) / Phase 1	A Trial to Assess the Safety and Tolerability of Repeated Doses of Intravitreal Administration of Two VEGF Trap Formulations in Subjects with Neovascular Age Related Macular Degeneration C.L.E.A.R. - Clinical Evaluation of Anti-angiogenesis in the Retina Intravitreal Trial (CLEAR-IT 1b)	nAMD Patients	4 mg IVT Q4W to Week 12, after Week 12, 4mg PRN (N=6 ITV-1; N=10 ITV-2) 8 mg 1 st dose, then 4 mg Q4W to Week 12, after Week 12, 4mg PRN (N=3 ITV-2; 8 mg was not the intended study dose) Note: Fellow eye treatment was allowed during the study	Screening, pre-dose, Weeks 4, 8, 12, 16, 20 24, 28, 32, 36, 40, 44, 48, and 52
VGFT-OD-0702.PK / Phase 2	VEGF Trap-Eye Pharmacokinetic Sub-study (PK Sub-Study of VGFT-OD-0702)	nAMD Patients	2mg IVT Q8W (N=5) Note: Fellow eye treatment was allowed during the study	Pre-dose, 4h, 8h, Days 2, 3, 4, 5, 8, 15, and 29
VGFT-OD-0706.PK / Phase 2	Pharmacokinetic Sub-Study of Intravitreally Administered VEGF Trap-Eye in Subjects with DME (PK Sub-Study of VGFT-OD-0706 [DA VINCI])	DME Patients	2mg IVT SD (N=4) 0.5 mg IVT SD (N=2, not the intended PK sub-study dose) 2 of the 8 patients enrolled in PK sub-study received a sham PK sub-study dose. Note: Fellow eye treatment was allowed during the study	Pre-dose, 4h, 8h, Days 2, 3, 4, 5, 8, 15, and 29

Study Number/Phase	Study Title	Study Population	Dosing Regimens	Pharmacokinetic Sampling Schedule
311523 (VIEW2) / Phase 3	A randomized, double masked, active controlled, phase 3 study of the efficacy, safety, and tolerability of repeated doses of intravitreal VEGF Trap-Eye in subjects with neovascular age-related macular degeneration (AMD)	nAMD Patients	0.5 mg IVT Q4W (N=175) 2 mg IVT Q4W (N=181) 2 mg IVT Q8W: With 3 Q4W initial doses (N=175) Note: Fellow eye treatment was allowed during the study	Pre-dose and post-dose (1 to 4 hours post-dose) at Week 0 (Baseline) and Week 48; pre-dose only on Weeks 1, 4, 12, and 52
91745 (VIVID) / Phase 3	A randomized, double masked, active controlled, phase III study of the efficacy and safety of repeated doses of intravitreal VEGF Trap-Eye in subjects with diabetic macular edema	DME Patients	2 mg IVT Q4W (N=136) 2mg IVT Q8W: With 5 Q4W initial doses (N=134) Laser Coagulation PRN and allowed VEGF Trap-Eye injections year 3 only; 2 mg IVT PRN (N=31 received aflibercept after laser treatment with PK sampled after aflibercept dose) Note: Fellow eye treatment was allowed during the study	Pre-dose and post-dose (1 to 4 hours post-dose) at Week 0 (Baseline), Days 2 to 4, Weeks 24 and 52

Study Number/Phase	Study Title	Study Population	Dosing Regimens	Pharmacokinetic Sampling Schedule
VGFTe (HD)-AMD-1905 (CANDELA) / Phase 2	A Randomized, Single-Masked, Active-Controlled Phase 2 Study of the Safety, Tolerability, and Efficacy of Repeated Doses of High-Dose Aflibercept in Patients with Neovascular Age-Related Macular Degeneration	nAMD patients	2 mg IVT Q12W: With 3 Q4W initial doses (N=52) 8 mg IVT Q12W: With 3 Q4W initial doses (N=53) Note: Fellow eye treatment was allowed during the study with 2mg dose of aflibercept	Predose, 4h ^a , 8h ^a , Days 2 ^a , 3 ^a , 5 ^a , 8 ^a , 15 ^a , 22 ^a , 29, 57, 61, 85, 113, 141, 169, 225, and 309
VGFTe-HD-DME-1934 (PHOTON) / Phase 2/3	A Randomized, Double-Masked, Active-Controlled Phase 2/3 Study of the Efficacy and Safety of High-Dose Aflibercept in Patients with Diabetic Macular Edema	DME patients	2 mg IVT Q8W: With 5 Q4W initial doses (N=163) 8 mg IVT Q12W: With 3 Q4W initial doses (N=323) 8 mg IVT Q16W: With 3 Q4W initial doses (N=162) Note: Fellow eye treatment was allowed during the study with 2mg dose of aflibercept	Predose, 4h ^a , 8h ^a , Days 2 ^a , 3 ^a , 5 ^a , 8 ^a , 15 ^a , 22 ^a , 29, 60-64, 85, 197, and 337

Study Number/Phase	Study Title	Study Population	Dosing Regimens	Pharmacokinetic Sampling Schedule
86-5321-20968 (PULSAR) / Phase 3	Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of High Dose Aflibercept in Patients With Neovascular Age-Related Macular Degeneration	nAMD patients	2 mg IVT Q8W: With 3 Q4W initial doses (N=308) 8 mg IVT Q12W: With 3 Q4W initial doses (N=313) 8 mg IVT Q16W: With 3 Q4W initial doses (N=312) Note: Fellow eye treatment was allowed during the study with 2mg dose of aflibercept	Predose, 4h ^a , 8h ^a , Days 2 ^a , 3 ^a , 5 ^a , 8 ^a , 15 ^a , 22 ^a , 29, 60-64, 85, 197, and 337

^aOnly collected in PK sub-study

DME = Diabetic macular edema; IV = Intravenous; IVT = Intravitreal; N = Number of patients, nAMD = Neovascular age-related macular degeneration; PRN = Pro re nata (as needed); Q2W = Every 2 weeks; Q4W = Every 4 weeks; Q8W = Every 8 weeks; Q12W = Every 12 weeks; Q16W = Every 16 weeks; SC = Subcutaneous; SD = Single dose

Source: Applicant's poppk report, Page 43-49 ([link](#)).

Table 30. Summary of Baseline Demographic Covariates for Analysis

	nAMD Patients (N=1662)	DME Patients (N=967)	Healthy Subject (N=76)	Oncology Patient (N=38)	Overall (N=2743)
Administration Route					
IV	22 (1.3%)	6 (0.6%)	36 (47.4%)	0 (0%)	64 (2.3%)
IVT	1640 (98.7%)	961 (99.4%)	0 (0%)	0 (0%)	2601 (94.8%)
IV + SC	0 (0%)	0 (0%)	40 (52.6%)	0 (0%)	40 (1.5%)
SC	0 (0%)	0 (0%)	0 (0%)	38 (100%)	38 (1.4%)
Age (years)					
Mean (SD)	75.0 (8.26)	62.8 (9.80)	30.8 (8.90)	56.3 (13.9)	69.2 (12.6)
Median [Min, Max]	76.0 [50.0, 97.0]	63.0 [24.0, 90.0]	30.0 [18.0, 45.0]	60.0 [23.0, 75.0]	71.0 [18.0, 97.0]
Body Weight (kg)					
Mean (SD)	75.1 (16.8)	84.9 (19.9)	76.4 (8.02)	77.7 (19.9)	78.6 (18.4)
Median [Min, Max]	72.7 [38.1, 164]	82.0 [40.8, 167]	75.3 [59.6, 101]	78.9 [41.3, 121]	76.0 [38.1, 167]
Missing	5 (0.3%)	0 (0%)	0 (0%)	0 (0%)	5 (0.2%)
Estimated Glomerular Filtration Rate (mL/min/1.73 m²)					
Mean (SD)	72.9 (16.4)	79.5 (25.2)	110 (17.4)	79.4 (19.2)	76.4 (21.0)
Median [Min, Max]	74.6 [18.2, 121]	84.0 [5.19, 146]	111 [75.8, 145]	76.9 [41.1, 133]	78.1 [5.19, 146]
Alanine Transaminase, ALT (U/L)					
Mean (SD)	20.2 (11.5)	21.6 (12.3)	21.6 (9.58)	20.3 (11.4)	20.7 (11.8)
Median [Min, Max]	17.0 [2.00, 157]	19.0 [5.00, 175]	19.5 [9.00, 50.0]	18.0 [7.00, 59.0]	18.0 [2.00, 175]
Aspartate Aminotransferase, AST (U/L)					
Mean (SD)	22.5 (9.70)	20.9 (9.89)	21.3 (6.13)	21.9 (6.06)	21.9 (9.67)
Median [Min, Max]	21.0 [10.0, 205]	19.0 [7.00, 189]	21.0 [8.00, 39.0]	22.0 [11.0, 39.0]	20.0 [7.00, 205]

	nAMD Patients (N=1662)	DME Patients (N=967)	Healthy Subject (N=76)	Oncology Patient (N=38)	Overall (N=2743)
Albumin (g/dL)					
Mean (SD)	4.35 (0.335)	4.26 (0.434)	NA (NA)	3.72 (0.450)	4.31 (0.385)
Median [Min, Max]	4.40 [3.00, 5.60]	4.30 [1.90, 5.40]	NA [NA, NA]	3.70 [2.60, 4.70]	4.30 [1.90, 5.60]
Missing	0 (0%)	0 (0%)	76 (100%)	0 (0%)	76 (2.8%)
Alkaline Phosphatase, ALP (U/L)					
Mean (SD)	77.7 (25.4)	80.1 (26.5)	68.4 (18.1)	106 (98.8)	78.7 (28.2)
Median [Min, Max]	74.0 [9.00, 334]	75.0 [15.0, 261]	66.0 [34.0, 120]	82.0 [45.0, 650]	74.5 [9.00, 650]
Bilirubin (μmol/L)					
Mean (SD)	0.511 (0.293)	0.421 (0.246)	0.724 (0.248)	NA (NA)	0.485 (0.282)
Median [Min, Max]	0.409 [0.0731, 3.68]	0.351 [0.0877, 2.13]	0.700 [0.304, 1.76]	NA [NA, NA]	0.409 [0.0731, 3.68]
Missing	0 (0%)	7 (0.7%)	0 (0%)	38 (100%)	45 (1.6%)
Race					
AMERICAN INDIAN OR ALASKA NATIVE	1 (0.1%)	2 (0.2%)	0 (0%)	0 (0%)	3 (0.1%)
ASIAN	263 (15.8%)	160 (16.5%)	0 (0%)	0 (0%)	423 (15.4%)
BLACK	5 (0.3%)	64 (6.6%)	5 (6.6%)	0 (0%)	74 (2.7%)
MISSING	42 (2.5%)	0 (0%)	0 (0%)	0 (0%)	42 (1.5%)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (0.1%)	1 (0.1%)	0 (0%)	1 (2.6%)	3 (0.1%)
NOT REPORTED	5 (0.3%)	9 (0.9%)	0 (0%)	0 (0%)	14 (0.5%)
OTHER	3 (0.2%)	12 (1.2%)	4 (5.3%)	2 (5.3%)	21 (0.8%)
WHITE	1342 (80.7%)	719 (74.4%)	67 (88.2%)	35 (92.1%)	2163 (78.9%)
Sex					
F	952 (57.3%)	372 (38.5%)	0 (0%)	19 (50.0%)	1343 (49.0%)
M	710 (42.7%)	595 (61.5%)	76 (100%)	19 (50.0%)	1400 (51.0%)

	nAMD Patients (N=1662)	DME Patients (N=967)	Healthy Subject (N=76)	Oncology Patient (N=38)	Overall (N=2743)
Japanese					
N	1489 (89.6%)	838 (86.7%)	76 (100%)	38 (100%)	2441 (89.0%)
Y	173 (10.4%)	129 (13.3%)	0 (0%)	0 (0%)	302 (11.0%)
Hispanic/Latino Ethnicity					
HISPANIC OR LATINO	82 (4.9%)	116 (12.0%)	0 (0%)	1 (2.6%)	199 (7.3%)
MISSING	12 (0.7%)	15 (1.6%)	76 (100%)	2 (5.3%)	105 (3.8%)
NOT HISPANIC OR LATINO	1568 (94.3%)	836 (86.5%)	0 (0%)	35 (92.1%)	2439 (88.9%)
Urine Protein Category					
1+	91 (5.5%)	42 (4.3%)	0 (0%)	0 (0%)	133 (4.8%)
2+	14 (0.8%)	22 (2.3%)	0 (0%)	0 (0%)	36 (1.3%)
3+	4 (0.2%)	19 (2.0%)	0 (0%)	0 (0%)	23 (0.8%)
MISSING	137 (8.2%)	651 (67.3%)	76 (100%)	38 (100%)	902 (32.9%)
NEGATIVE	1224 (73.6%)	165 (17.1%)	0 (0%)	0 (0%)	1389 (50.6%)
TRACE	192 (11.6%)	67 (6.9%)	0 (0%)	0 (0%)	259 (9.4%)
4+	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)	1 (0.0%)
Renal Impairment Category					
NORMAL	423 (25.5%)	485 (50.2%)	75 (98.7%)	0 (0%)	983 (35.8%)
MILD	899 (54.1%)	311 (32.2%)	1 (1.3%)	0 (0%)	1211 (44.1%)
MODERATE	326 (19.6%)	141 (14.6%)	0 (0%)	0 (0%)	467 (17.0%)
SEVERE	9 (0.5%)	23 (2.4%)	0 (0%)	0 (0%)	32 (1.2%)
RENAL FAILURE	0 (0%)	7 (0.7%)	0 (0%)	0 (0%)	7 (0.3%)
MISSING	5 (0.3%)	0 (0%)	0 (0%)	38 (100%)	43 (1.6%)
Hepatic Impairment Category					
MILD	103 (6.2%)	47 (4.9%)	5 (6.6%)	0 (0%)	155 (5.7%)
MISSING	12 (0.7%)	24 (2.5%)	0 (0%)	38 (100%)	74 (2.7%)
MODERATE	7 (0.4%)	4 (0.4%)	0 (0%)	0 (0%)	11 (0.4%)
NORMAL	1539 (92.6%)	892 (92.2%)	71 (93.4%)	0 (0%)	2502 (91.2%)

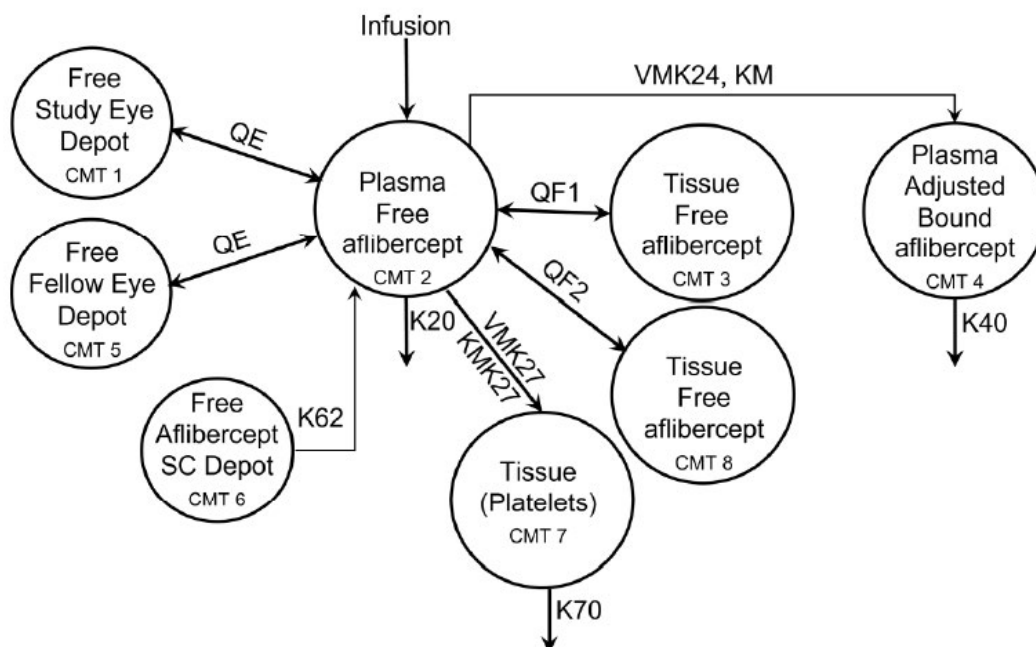
	nAMD Patients (N=1662)	DME Patients (N=967)	Healthy Subject (N=76)	Oncology Patient (N=38)	Overall (N=2743)
SEVERE	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.0%)
Fellow Eye Treatment with Aflibercept					
Yes	212 (12.8%)	398 (41.2%)	0 (0%)	0 (0%)	610 (22.2%)
No	1450 (87.2%)	569 (58.8%)	76 (100%)	38 (100%)	2133 (77.8%)
Note: Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation. Renal function was categorized based upon eGFR values multiplied by individual body surface area and divided by 1.73.					

Source: Applicant's poppk report , Page 15-18 ([link](#)).

Base model

The base model is a three-compartment PK model for free aflibercept, including a Michaelis-Menten type binding of free aflibercept to VEGF occurring from the central compartment of free aflibercept, and the addition of a tissue compartment with saturable elimination from the central compartment adequately described the nonlinear disposition process of aflibercept following IV and SC administration, shown in Figure 23.

Figure 23. Structural Representation of a Population Pharmacokinetic Model



CMT = compartment; IV = intravenous; IVT = intravitreal; QE = inter-compartmental clearance between ocular compartment and central compartment of free aflibercept; K62 = rate of absorption from subcutaneous injection depot compartment; K20 = elimination rate constant for free aflibercept; QF1 and QF2 = inter-compartmental clearances of free aflibercept; K40 = elimination rate constant for adjusted bound aflibercept; K70 = elimination rate constant from tissue (platelet) compartment; VMK24, KM = saturable Michaelis-Menten type binding of free aflibercept with VEGF; VMK27, KMK27 = saturable elimination from plasma compartment to tissue compartment (platelets)
 Note: CMT 2 and CMT 4 are both representative of the plasma compartment and volumes are assumed to be equal.

Source: Applicant's poppk report , Page 18 ([link](#)).

Reviewer's comment:

In the differential equation, there is a semi-mechanistical model $((VMK27 \cdot V_2) \cdot (1 - A(7)) / (KMK27 + A(7))) \cdot A(2)$, in which VMK27 is maximum binding rate of aflibercept to platelets; $A(2)$ is the free aflibercept plasma concentration (compartment 2); $A(7)$ is adjusted bound aflibercept concentration (compartment 7, platelets); KMK27 is the concentration of free aflibercept at half of maximum binding capacity to platelets.¹ Some of parameter definitions in the PopPK structure model (Figure 23) are different from those of parameter estimates for final PopPK model². Meanwhile, the compartment of SC was set to be 8 in the NONME dataset³, while the compartment of SC is 6 in the model structure (Figure 23). Although there are some inconsistencies in the PopPK report, it does not affect the performance or assessment of the final model.

Inter-individual variability was modelled assuming a log-normal distribution for patient level random effects. The inter-individual variability was included on central volume distribution for free aflibercept (V_2)

¹ Source: Applicant's poppk report , Page 297 ([link](#)).

² Source: Applicant's poppk report , Page 75 ([link](#)).

³ Source: Applicant's poppk report , Page 178 (CMT=8 for SC dosing) ([link](#)).

and adjusted bound aflibercept (V4), the elimination rate constants of free aflibercept (K20) and adjusted bound aflibercept (K40), maximum binding rate of free aflibercept to VEGF (VMK24), inter-compartmental clearance between the ocular compartment and the central compartment of free aflibercept (QE), the absorption rate constant for SC injection (K62) and the bioavailability of SC injections (F6).

Intra-individual variability was tested as combined additive and proportional error model on the dependent variable for free and adjusted bound aflibercept.

Model evaluation and selection were based on the point estimates of PK parameters, their respective relative standard errors and standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), successful model convergence, bootstrap, and diagnostic prediction-corrected visual predictive check (PcVPC).

Covariate analysis

Covariate parameters include body size measurements (body weight, body mass index (BMI), lean body weight (LBW), and Fat mass (FM)) were assessed as covariates for volume and clearance parameters. The other covariates displayed in Table 31 were then investigated and time-varying covariates, e.g., food status and formulation, were evaluated separately after the automated covariate search.

Table 31. Covariate analysis: covariates that were assessed

Parameter	Covariates
k ₂₀	Age, sex, patient population (DME, AMD), ALB, creatinine clearance, hepatic dysfunction categories (0 = Normal, Mild = 1, Moderate = 2, Severe = 3)
V2	Age, sex, body weight, patient population (DME, AMD), ALB
k ₁₂ , k ₅₂	Age, patient population (DME, AMD)

ALB = Albumin; k₂₀, k₄₀ = Rate of elimination; V2 = Central volume of distribution for free drug; k₁₂, k₅₂ = Rate of absorption from vitreous humor; hepatic dysfunction categories based on National Cancer Institute – Organ Dysfunction Working Group criteria (Patel, 2004)

Source: Applicant's poppk report, Page 424 ([link](#)).

Software and estimation methods

PK of aflibercept will be characterized by nonlinear mixed-effects modeling using NONMEM® (b) (4) The first-order conditional estimation (FOCE) with INTERACTION method in NONMEM® was utilized.

1.4 Final Model

The parameter estimates for the final PopPK model are listed in Table 32. The prediction corrected VPC plot for the final covariate model with all data is shown in Figure 24 (Stratified by dose and study).

- A 3-compartment model of the PK of aflibercept and its nonlinear binding to VEGF with an additional nonlinear clearance pathway was able to describe the observed free and adjusted bound aflibercept data after IVT administration in patients with nAMD and DME.

- The PopPK model identified age and the HD drug product effect (high dose [8 mg cohorts] vs. lower doses [≤ 4 mg cohorts]) as significant predictors of clearance of aflibercept from the ocular compartment (QE), body weight as a predictor of systemic volumes ($V_2 = V_4, V_3, V_8$) and rates of elimination (K20, K40), and albumin as a predictor of the rate of elimination for adjusted bound (K40).
- Exposures of free aflibercept for participants in the lowest (38.1 – 64.5 kg) and highest (97.5 - 167 kg) quintile of body weight were predicted to be 27-39% higher and 16-31% lower, respectively, than the participants in the reference group (73.5 – 83.5 kg). The body weight differences across renal insufficiency categories also accounted for exposure differences across those categories. There were no relevant differences found in the exposure metrics of aflibercept between age categories, albumin categories, hepatic function categories, Asian and non-Asian, or Japanese and non-Japanese participants. Differences in the body weight of Asians or Japanese accounted for the small differences in AUC and C_{max}. After accounting for an age effect on QE, no significant difference in the PK was found between nAMD and DME populations.
- The HD (8 mg) dose was estimated to have 34.3% slower QE and 1.52 times longer half-life from the ocular compartment than the lower dose groups.

Table 32. Population Pharmacokinetic Parameter Estimates for Final Models

Parameter	Estimate	C.I.95	RSE %	CV %
K20 (1/day) [run431 Estimate]	0.0807	0.0438 — 0.136	29.5	—
V2 V4 (L) [run431 Estimate]	4.99	4.71 — 5.25	2.79	—
V3 (L) [run431 Estimate]	1.08	0.816 — 1.58	17	—
QF1 (L/day) [run431 Estimate]	0.849	0.435 — 1.33	29.2	—
V8 (L) [run431 Estimate]	1.18	0.281 — 0.541	16.8	—
QF2 (L/day) [run431 Estimate]	0.0763	0.147 — 0.186	5.93	—
KM (mg/L) [run431 Estimate]	0.411	0.293 — 0.442	10.5	—
VMK24 (mg/day/L) [run431 Estimate]	0.167	0.482 — 0.593	—	—
K40 (1/day) [run463 Estimate]	0.035	—	—	—
F1 & F5	0.719	0.706 — 0.731	—	—
QE (L/day)	0.000624	0.000577 — 0.000674	3.97	—
K62 (1/day) [run431 Estimate]	0.368	0.0165 — 0.0632	35.3	—
F6 [run431 Estimate]	0.536	0.00584 — 0.149	99	—
VMK27 (mg/day/L) [run431 Estimate]	0.031	4.17 — 340	159	—
K70 (1/day) [run431 Estimate]	0.0265	0.632 — 2.84	39.8	—
KMK27 (mg) [run431 Estimate]	42.7	0.0481 — 0.12	23.7	—
TWGT V2+V4 [run431 Estimate]	0.872	0.55 — 1.22	19.3	—
TWGT V3 [run431 Estimate]	1.08	-0.00762 — 2.45	51.3	—
TWGT V8 [run431 Estimate]	1.16	-2.97 — 6.58	135	—
TWGT K20 [run431 Estimate]	-0.192	-1.28 — 0.819	234	—
TWGT K40 [run463 Estimate]	-0.153	—	—	—
HD QE	0.657	0.607 — 0.712	4.08	—
AGE QE	-1.53	-1.76 — -1.3	7.68	—
TALB K40 [run463 Estimate]	-0.767	—	—	—
IIV K20 [run431 Estimate]	0.207	-0.0147 — 0.508	54.1	48
IIV covariance(K20, V2 & V4) [run431 Estimate]	-0.0727	-0.136 — -0.0183	38.9	—
IIV V2 & V4 [run431 Estimate]	0.0618	0.0198 — 0.105	34.7	25.3
IIV VMK24 [run431 Estimate]	0.305	-0.083 — 0.67	65.4	59.8
IIV K40 [run463 Estimate]	0.0452	—	—	21.5
IIV QE	0.297	0.257 — 0.336	6.86	58.8
IIV K62 [run431 Estimate]	0.852	0.124 — 1.45	43	116
IIV F6 [run431 Estimate]	0.629	0.288 — 0.905	26.4	93.6

Parameter	Estimate	C.I.95	RSE %	CV %
SD ADD LLOQ 0.0313 (Free,IV+SC) [run463 Estimate]	0.025	—	—	—
SD PROP LLOQ 0.0313 (Free,IV+SC) [run463 Estimate]	0.403	—	—	—
SD ADD LLOQ 0.0156 (Free)	0.00779	0.00624 — 0.00973	11.4	—
SD PROP LLOQ 0.0156 (Free)	0.433	0.418 — 0.448	1.72	—
SD ADD LLOQ 0.0315 (Adj.Bound)	0.0216	0.0177 — 0.0264	10.2	—
SD PROP LLOQ 0.0315 (Adj.Bound)	0.159	0.12 — 0.197	12.4	—
SD ADD LLOQ 0.0224 (Adj.Bound)	0.0291	0.0202 — 0.0419	18.8	—
SD PROP LLOQ 0.0224 (Adj.Bound)	0.214	0.194 — 0.234	4.83	—

Age = baseline age; C.I.95 = 95% confidence intervals; CV% = coefficient of variation as a percentage; F1 and F5 = bioavailability of intravitreal injections in ocular compartments; F6 = bioavailability of subcutaneous injections; HD = high dose (8 mg IVT cohorts); IIV = inter-subject variability; K20 = elimination rate constant for free aflibercept; K40 = elimination rate constant for adjusted bound aflibercept; K62 = rate of absorption from subcutaneous injection dosing compartment; K70 = elimination rate constant from tissue (platelet) compartment; KM = concentration of free aflibercept at half of maximum binding capacity with VEGF; KMK27 = concentration of free aflibercept at half of maximum binding capacity to platelets; QE = inter-compartmental clearance between ocular compartment and central compartment of free aflibercept; QF1 and QF2 = inter-compartmental clearances of free aflibercept; RSE% = percent relative standard error; TALB = time varying albumin; TWGT = time varying body weight; V2 = central volume of free aflibercept in plasma; V4 = central volume of adjusted bound aflibercept in plasma; V3 and V8 = peripheral volumes of free aflibercept in tissues; VMK24 = maximum binding rate of free aflibercept to VEGF; VMK27 = maximum binding rate of aflibercept to platelets

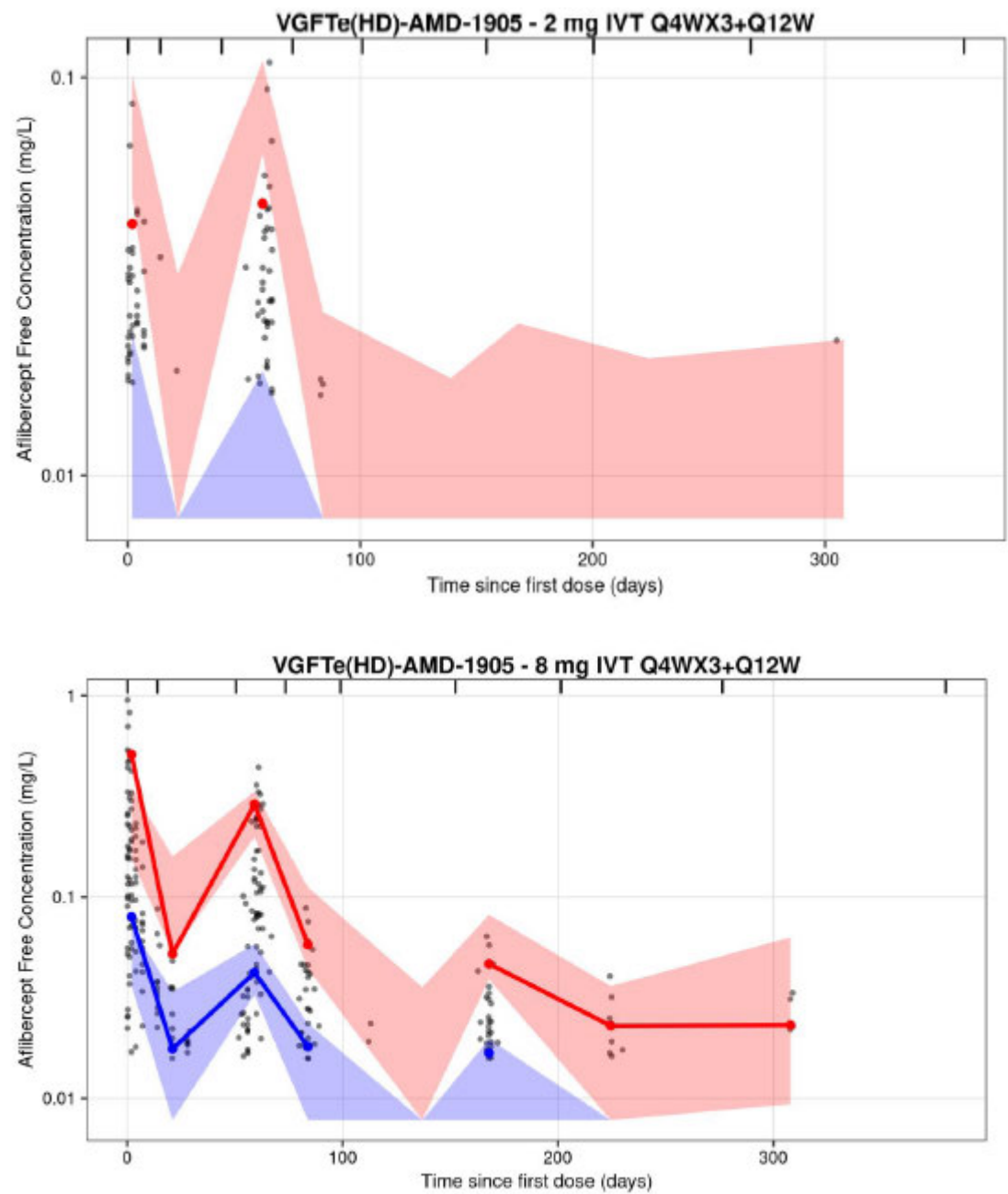
Note: Estimates of fixed-effect parameters are presented in the natural scale; IIV are reported as variances around the log of the parameters or the logit of F6. Residual errors of IV and SC data not presented in the table for LLOQ=0.0156 ($\sigma_{\text{additive}}=0.00786$, $\sigma_{\text{proportional}}=0.357$) and LLOQ=0.0315 ($\sigma_{\text{additive}}=0.0206$, $\sigma_{\text{proportional}}=0.167$) were fixed in the final model to estimates from run463. C.I.95 and RSE% for run431 were calculated from bootstrap. η -shrinkage: $\eta_{K20}=54.2\%$, $\eta_{V2,V4}=15.2\%$, $\eta_{VMK24}=42.2\%$, $\eta_{K40}=39.1\%$, $\eta_{QE}=31.6\%$, $\eta_{K62}=1e-10\%$, $\eta_{F6}=17.7\%$.

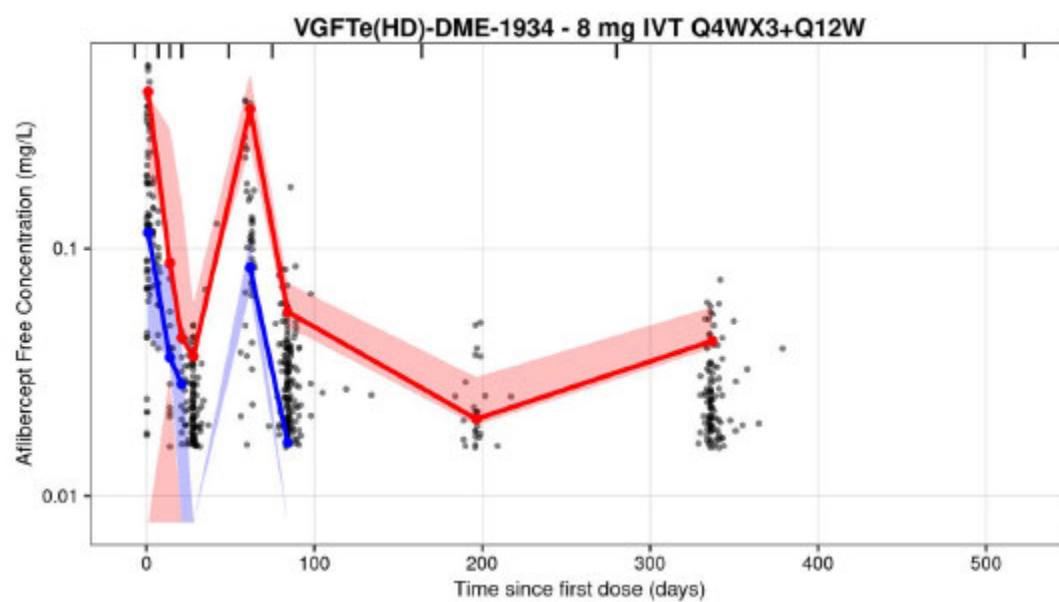
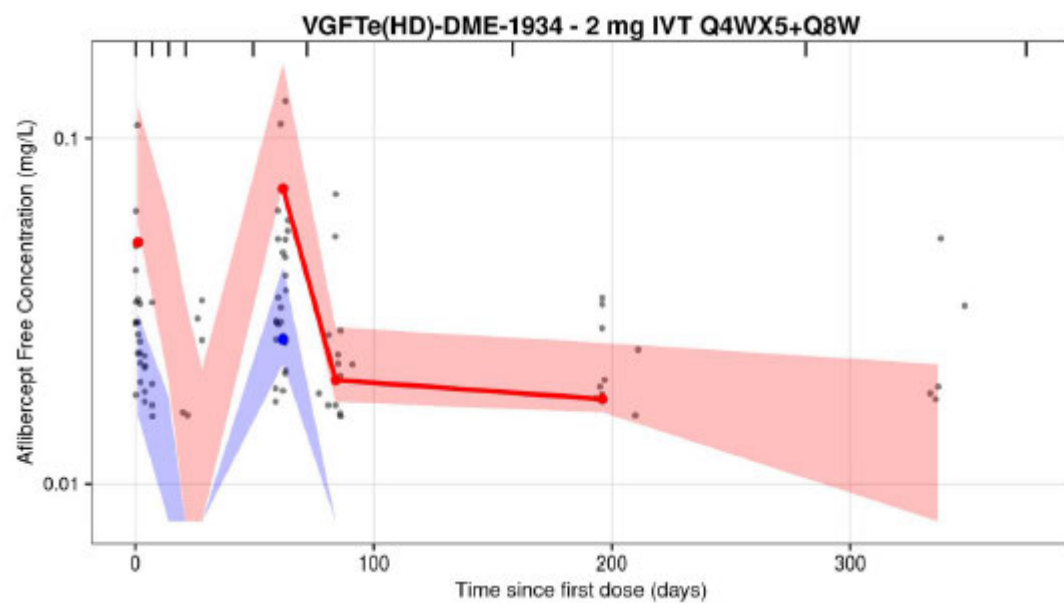
Typical values of model parameters are calculated as:

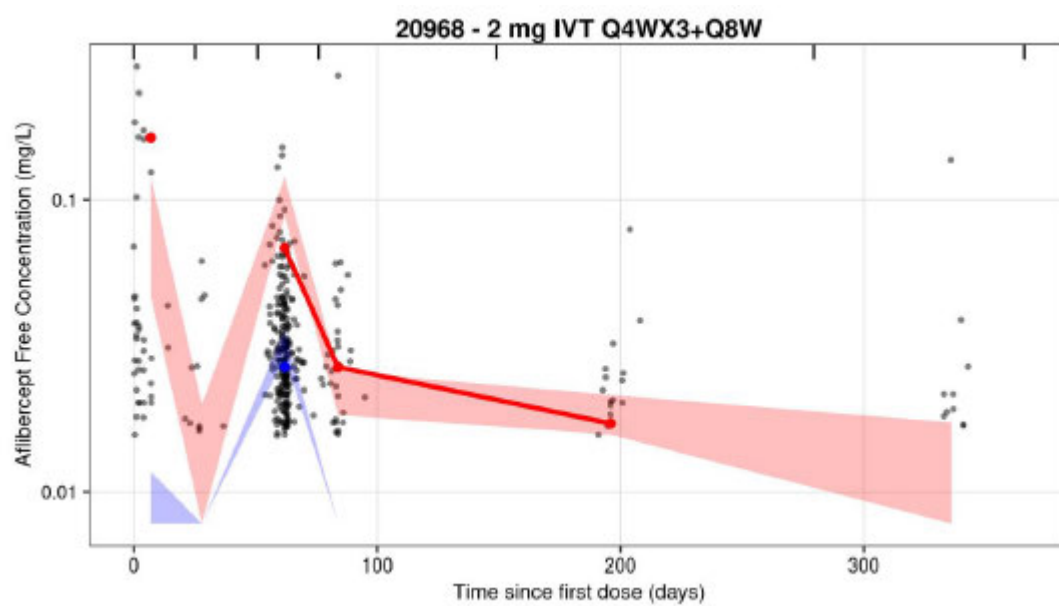
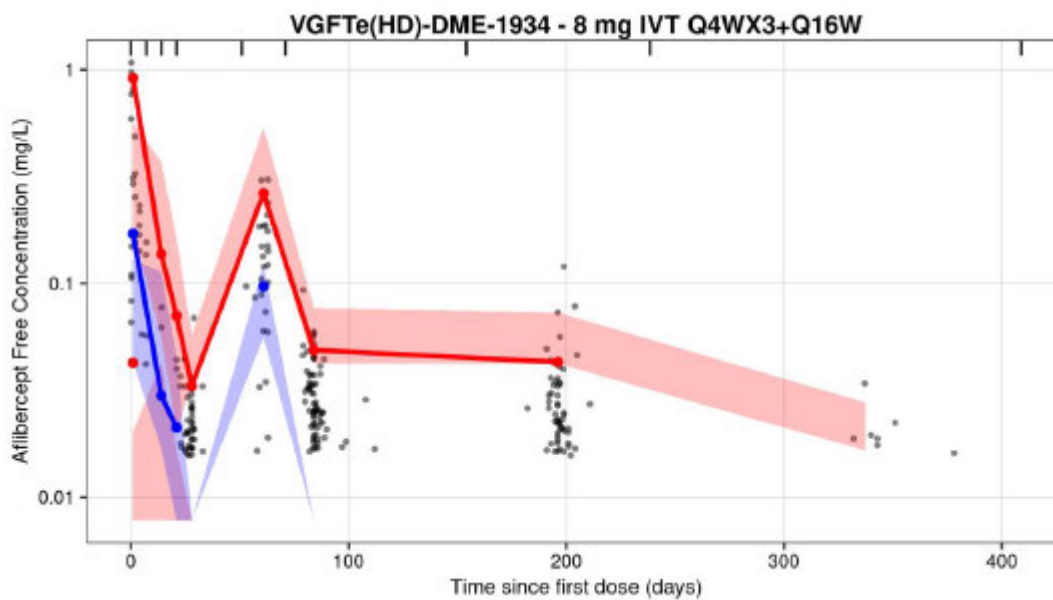
$$\begin{aligned}
 QE &= 0.000624 \times 0.657^{HD} \times \left(\frac{Age}{71}\right)^{-1.53} \quad \text{where HD=1 for 8 mg IVT cohorts and 0 for } \leq 4 \text{ mg IVT cohorts} \\
 V2 &= V4 = 4.99 \times \left(\frac{TWGT}{76}\right)^{0.872} \\
 V3 &= 1.08 \times \left(\frac{TWGT}{76}\right)^{1.08} \\
 V8 &= 1.18 \times \left(\frac{TWGT}{76}\right)^{1.16} \\
 K20 &= 0.0807 \times \left(\frac{TWGT}{76}\right)^{-0.192} \\
 K40 &= 0.035 \times \left(\frac{TWGT}{76}\right)^{-0.153} \times \left(\frac{TALB}{4.3}\right)^{-0.767}
 \end{aligned}$$

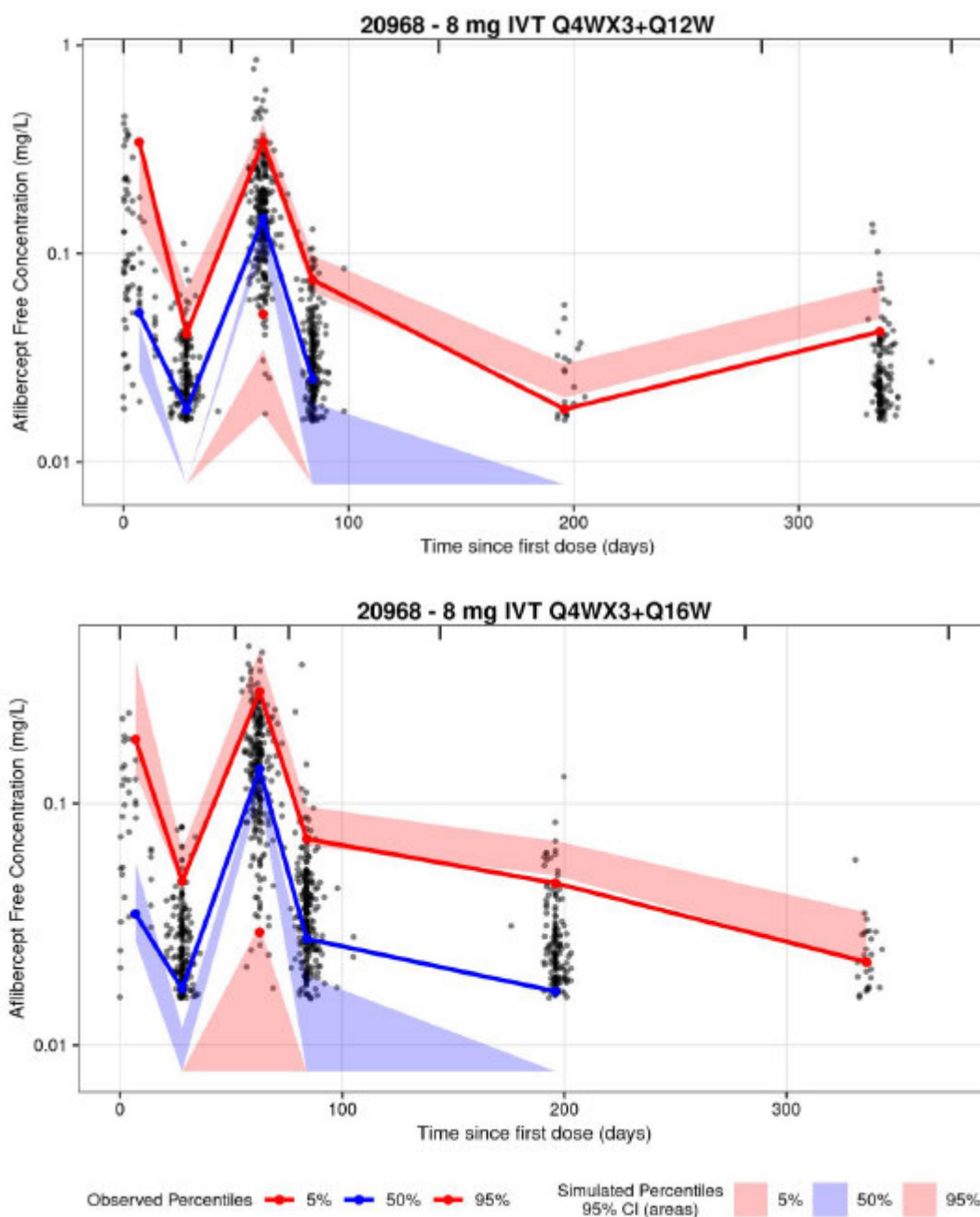
Source: Applicant's poppk report, Page 20-21 ([link](#)).

Figure 24. Prediction-Corrected VPC Stratified by dose and study









Source: Applicant's poppk report, Page 23-30 ([link](#)).

1.5 simulation

The effect of age, body weight, albumin concentration, renal function, hepatic function, racial group, Japanese origin, and population on aflibercept PK was evaluated in participants from studies PHOTON, PULSAR, and CANDELA. Post hoc estimates of PK parameters in participants of these 3 studies and the individual values of the aforementioned variables were used in model-based simulation to predict exposure metrics for 3 different IVT dosing regimens (2q8, HDq12, and HDq16).

The PopPK model identified age as a statistically significant covariate on ocular clearance. Regardless of the tested dose regimens, the post hoc geometric mean of AUC_{tau}, C_{max,week56-60}, and C_{max,week8-12} in the different categories of age were calculated and shown in Table 33, Table 34 and Table 35. The differences of geometric mean of AUC_{tau}, C_{max,week56-60}, and C_{max,week8-12} are less than 20%, which is not clinically meaningful.

Table 33. Summary of Post Hoc Model-Predicted Exposure Metrics for the 2q8 Dosing Regimen, Stratified by Tertile of Age in Participants from Studies PHOTON, PULSAR, and CANDELA

Age (years)	N	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max,week56-60} (mg/L)	C _{max,week8-12} (mg/L)
Free aflibercept					
[24, 66)	524	89 (22.8%)	0.414 (38.9%)	0.0479 (54.8%)	0.0486 (54%)
[66, 76)	588	80.9 (23.5%)	0.463 (57.3%)	0.0422 (52.3%)	0.0437 (51.8%)
[76, 97]	574	73.5 (21.3%)	0.489 (38.2%)	0.0396 (53.5%)	0.0417 (50.9%)
Adjusted bound aflibercept					
[24, 66)	524	89 (22.8%)	4.86 (42.4%)	0.134 (37.1%)	0.185 (36.6%)
[66, 76)	588	80.9 (23.5%)	5.97 (52.4%)	0.155 (45.4%)	0.217 (44%)
[76, 97]	574	73.5 (21.3%)	6.55 (36.9%)	0.165 (34.1%)	0.234 (33.5%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max,week8-12} = maximum concentration from weeks 8 to 12, C_{max,week56-60} = maximum concentration from weeks 56 to 60, 2q8 = 2 mg aflibercept every 8 weeks following 5 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming 2q8 dosing for all participants.

[or] indicates that the respective limit is included in the interval;) indicates that the respective limit is not included in the interval

Source: Applicant's poppk report , Page 111 ([link](#)).

Table 34. Summary of Post Hoc Model-Predicted Exposure Metrics for the HDq12 Dosing Regimen, Stratified by Tertile of Age in Participants from Studies PHOTON, PULSAR, and CANDELA

Age (years)	N	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max,week56-60} (mg/L)	C _{max,week8-12} (mg/L)
Free aflibercept					
[24, 66)	524	89 (22.8%)	1.81 (41.7%)	0.157 (62.6%)	0.166 (59.5%)
[66, 76)	588	80.9 (23.5%)	2.01 (62.1%)	0.136 (59.7%)	0.151 (56.7%)
[76, 97]	574	73.5 (21.3%)	2.11 (41.4%)	0.126 (60.9%)	0.147 (53.5%)
Adjusted bound aflibercept					
[24, 66)	524	89 (22.8%)	18.5 (42.6%)	0.406 (35.4%)	0.663 (36%)
[66, 76)	588	80.9 (23.5%)	22.8 (51.6%)	0.461 (42.9%)	0.778 (42.7%)
[76, 97]	574	73.5 (21.3%)	25.2 (36.5%)	0.487 (33%)	0.839 (32.6%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max,week8-12} = maximum concentration from weeks 8 to 12, C_{max,week56-60} = maximum concentration from weeks 56 to 60, HDq12 = 8 mg aflibercept every 12 weeks following 3 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming HDq12 dosing for all participants.

[or] indicates that the respective limit is included in the interval;) indicates that the respective limit is not included in the interval

Source: Applicant's poppk report , Page 112 ([link](#)).

Table 35. Summary of Post Hoc Model-Predicted Exposure Metrics for the HDq16 Dosing Regimen, Stratified by Tertile of Age in Participants from Studies PHOTON, PULSAR, and CANDELA

Age (years)	N	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max,week56-60} (mg/L)	C _{max,week8-12} (mg/L)
Free aflibercept					
[24, 66)	524	89 (22.8%)	1.81 (41.7%)	0.156 (62.7%)	0.166 (59.5%)
[66, 76)	588	80.9 (23.5%)	2.01 (61%)	0.135 (59.7%)	0.151 (56.7%)
[76, 97]	574	73.5 (21.3%)	2.11 (41.4%)	0.126 (61.2%)	0.147 (53.5%)
Adjusted bound aflibercept					
[24, 66)	524	89 (22.8%)	18.5 (42.7%)	0.384 (34.6%)	0.663 (36%)
[66, 76)	588	80.9 (23.5%)	22.8 (51.9%)	0.431 (41.3%)	0.778 (42.7%)
[76, 97]	574	73.5 (21.3%)	25.2 (36.6%)	0.453 (32.7%)	0.839 (32.6%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max,week8-12} = maximum concentration from weeks 8 to 12, C_{max,week56-60} = maximum concentration from weeks 56 to 60, HDq16 = 8 mg aflibercept every 16 weeks following 3 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming HDq16 dosing for all participants.

[or] indicates that the respective limit is included in the interval;) indicates that the respective limit is not included in the interval

Source: Applicant's poppk report , Page 113 ([link](#)).

Body weight was a statistically significant predictor of systemic volume of distribution and rate of elimination for free and adjusted bound aflibercept and an increase in body weight was associated with a decrease in geometric mean of AUC_{tau}, C_{max,week56-60} and C_{max,week8-12}. In the lowest quintiles of body weight (38.1 to 64.5 kg), geometric means of AUC_{tau}, C_{max,week56-60} and C_{max,week8-12} were predicted to be 27 to 39% higher for free aflibercept and 25 to 27% higher for adjusted bound aflibercept compared to those in the reference quintile of body weight (73.5 to 83.5 kg). In the highest quintile of body weight (97.5 to 167 kg), geometric means of AUC_{tau}, C_{max,week56-60} and C_{max,week8-12} were predicted to be 16 to 31% lower for free aflibercept and 23 to 27% lower for adjusted bound aflibercept compared to those in the reference quintile of body weight, shown in Table 36, Table 37, and Table 38. Overall, this suggested that body weight at the lowest and highest quintiles exerts a modest influence on free and adjusted bound aflibercept exposures in plasma.

Table 36. Summary of Post Hoc Model-Predicted Exposure Metrics for the 2q8 Dosing Regimen, Stratified by Quintile of Weight in Participants from Studies PHOTON, PULSAR, and CANDELA

Weight (kg)	N	AUC _{tau} (mg x day/L)	C _{max,week56-60} (mg/L)	C _{max,week8-12} (mg/L)
Free aflibercept				
[38.1, 64.5)	337	0.615 (35.8%)	0.0534 (48.5%)	0.0556 (46.3%)
[64.5, 73.5)	334	0.518 (55.8%)	0.0453 (49.7%)	0.0472 (48.7%)
[73.5, 83.5)	339	0.442 (26.4%)	0.0417 (47.1%)	0.0431 (44.9%)
[83.5, 97.5)	336	0.399 (33.9%)	0.0401 (65.4%)	0.0411 (63.4%)
[97.5, 167]	340	0.312 (32.7%)	0.035 (50.2%)	0.0357 (48.9%)
Adjusted bound aflibercept				
[38.1, 64.5)	337	7.43 (45.6%)	0.193 (38.4%)	0.272 (37.4%)
[64.5, 73.5)	334	6.4 (41.4%)	0.165 (33.6%)	0.232 (32.6%)
[73.5, 83.5)	339	5.85 (38.7%)	0.152 (36.3%)	0.214 (35.7%)
[83.5, 97.5)	336	5.12 (33.4%)	0.135 (30.4%)	0.189 (30.1%)
[97.5, 167]	340	4.31 (44.5%)	0.115 (37.4%)	0.159 (35.2%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max,week8-12} = maximum concentration from weeks 8 to 12, C_{max,week56-60} = maximum concentration from weeks 56 to 60, 2q8 = 2 mg aflibercept every 8 weeks following 5 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming 2q8 dosing for all participants.

[or] indicates that the respective limit is included in the interval;) indicates that the respective limit is not included in the interval

Source: Applicant's poppk report, Page 117 ([link](#)).

Table 37. Summary of Post Hoc Model-Predicted Exposure Metrics for the HDq12 Dosing Regimen, Stratified by Quintile of Weight in Participants from Studies PHOTON, PULSAR, and CANDELA

Weight (kg)	N	AUC _{tau} (mg x day/L)	C _{max,week56-60} (mg/L)	C _{max,week8-12} (mg/L)
Free aflibercept				
[38.1, 64.5)	337	2.72 (39.2%)	0.175 (54.7%)	0.199 (48.4%)
[64.5, 73.5)	334	2.26 (60.1%)	0.146 (56.3%)	0.165 (52.3%)
[73.5, 83.5)	339	1.91 (28.3%)	0.134 (54.4%)	0.149 (47.8%)
[83.5, 97.5)	336	1.72 (37.8%)	0.128 (75.5%)	0.14 (68.8%)
[97.5, 167]	340	1.33 (33.7%)	0.111 (59.1%)	0.119 (54.4%)
Adjusted bound aflibercept				
[38.1, 64.5)	337	28.3 (46.2%)	0.567 (36.8%)	0.959 (37.7%)
[64.5, 73.5)	334	24.5 (40%)	0.489 (30.6%)	0.826 (30.3%)
[73.5, 83.5)	339	22.5 (39.2%)	0.455 (36.1%)	0.769 (36%)
[83.5, 97.5)	336	19.7 (33.1%)	0.404 (29%)	0.68 (29.1%)
[97.5, 167]	340	16.7 (45%)	0.349 (35.9%)	0.582 (35.4%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max,week8-12} = maximum concentration from weeks 8 to 12, C_{max,week56-60} = maximum concentration from weeks 56 to 60, HDq12 = 8 mg aflibercept every 12 weeks following 3 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming HDq12 dosing for all participants.

[or] indicates that the respective limit is included in the interval;) indicates that the respective limit is not included in the interval

Source: Applicant's poppk report , Page 118 ([link](#)).

Table 38. Summary of Post Hoc Model-Predicted Exposure Metrics for the HDq16 Dosing Regimen, Stratified by Quintile of Weight in Participants from Studies PHOTON, PULSAR, and CANDELA

Weight (kg)	N	AUC _{tau} (mg x day/L)	C _{max, week56-60} (mg/L)	C _{max, week8-12} (mg/L)
Free aflibercept				
[38.1, 64.5)	337	2.72 (39.2%)	0.175 (54.9%)	0.199 (48.4%)
[64.5, 73.5)	334	2.25 (58.6%)	0.146 (56.3%)	0.165 (52.3%)
[73.5, 83.5)	339	1.91 (28.3%)	0.134 (54.5%)	0.149 (47.8%)
[83.5, 97.5)	336	1.72 (37.8%)	0.128 (75.7%)	0.14 (68.8%)
[97.5, 167]	340	1.33 (33.6%)	0.111 (59.2%)	0.119 (54.4%)
Adjusted bound aflibercept				
[38.1, 64.5)	337	28.3 (46.3%)	0.532 (34.9%)	0.959 (37.7%)
[64.5, 73.5)	334	24.5 (40.5%)	0.457 (29.3%)	0.826 (30.3%)
[73.5, 83.5)	339	22.5 (39.2%)	0.426 (35.9%)	0.769 (36%)
[83.5, 97.5)	336	19.6 (33.2%)	0.379 (28.6%)	0.68 (29.1%)
[97.5, 167]	340	16.6 (45.1%)	0.327 (34.5%)	0.582 (35.4%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max, week8-12} = maximum concentration from weeks 8 to 12, C_{max, week56-60} = maximum concentration from weeks 56 to 60, HDq16 = 8 mg aflibercept every 16 weeks following 3 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming HDq16 dosing for all participants.

[or] indicates that the respective limit is included in the interval;) indicates that the respective limit is not included in the interval

Source: Applicant's poppk report , Page 119 ([link](#)).

The PopPK model identified serum albumin concentration as a statistically significant covariate. Comparisons of systemic exposure metrics by serum albumin concentration tertile suggest that the influence of this covariate on systemic exposure metrics of free and adjusted bound aflibercept resulted in only small numerical differences amongst the albumin tertiles, shown in Table 39, Table 40 and Table 41. Therefore, effect of albumin concentration on PK is not clinically meaningful.

Table 39. Summary of Post Hoc Model-Predicted Exposure Metrics for the 2q8 Dosing Regimen, Stratified by Serum Albumin Tertile in Participants from Studies PHOTON, PULSAR, and CANDELA

Albumin (g/dL)	N	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max,week56-60} (mg/L)	C _{max,week8-12} (mg/L)
Free aflibercept					
[2.5, 4.4)	532	83 (25.4%)	0.441 (37.7%)	0.0419 (55.5%)	0.0432 (53.6%)
[4.4, 4.6)	492	80 (23.8%)	0.454 (40.4%)	0.0418 (48.4%)	0.0433 (46.9%)
[4.6, 5.6]	662	80 (22.5%)	0.471 (55.3%)	0.045 (56.7%)	0.0465 (55.5%)
Adjusted bound aflibercept					
[2.5, 4.4)	532	83 (25.4%)	5.37 (40.7%)	0.143 (37.8%)	0.201 (37.7%)
[4.4, 4.6)	492	80 (23.8%)	5.87 (43.2%)	0.153 (37.6%)	0.215 (37.9%)
[4.6, 5.6]	662	80 (22.5%)	6.14 (50%)	0.158 (42.8%)	0.221 (41.4%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max,week8-12} = maximum concentration from weeks 8 to 12, C_{max,week56-60} = maximum concentration from weeks 56 to 60, 2q8 = 2 mg aflibercept every 8 weeks following 5 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming 2q8 dosing for all participants.

[or] indicates that the respective limit is included in the interval;) indicates that the respective limit is not included in the interval

Source: Applicant's poppk report , Page 123 ([link](#)).

Table 40. Summary of Post Hoc Model-Predicted Exposure Metrics for the HDq12Dosing Regimen, Stratified by Serum Albumin Tertile in Participants from Studies PHOTON, PULSAR, and CANDELA

Albumin (g/dL)	N	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max,week56-60} (mg/L)	C _{max,week8-12} (mg/L)
Free aflibercept					
[2.5, 4.4)	532	83 (25.4%)	1.91 (40.5%)	0.135 (63.5%)	0.149 (57.5%)
[4.4, 4.6)	492	80 (23.8%)	1.97 (43.4%)	0.134 (55.4%)	0.15 (51%)
[4.6, 5.6]	662	80 (22.5%)	2.06 (59.8%)	0.146 (64.6%)	0.161 (60.1%)
Adjusted bound aflibercept					
[2.5, 4.4)	532	83 (25.4%)	20.6 (41%)	0.43 (37.1%)	0.722 (37.5%)
[4.4, 4.6)	492	80 (23.8%)	22.5 (42.7%)	0.455 (35.5%)	0.769 (36.2%)
[4.6, 5.6]	662	80 (22.5%)	23.4 (49.7%)	0.469 (40.3%)	0.791 (40.5%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max,week8-12} = maximum concentration from weeks 8 to 12, C_{max,week56-60} = maximum concentration from weeks 56 to 60, HDq12 = 8 mg aflibercept every 12 weeks following 3 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming HDq12 dosing for all participants.

[or] indicates that the respective limit is included in the interval;) indicates that the respective limit is not included in the interval

Source: Applicant's poppk report , Page 124 ([link](#)).

Table 41. Summary of Post Hoc Model-Predicted Exposure Metrics for the HDq16 Dosing Regimen, Stratified by Serum Albumin Tertile in Participants from Studies PHOTON, PULSAR, and CANDELA

Albumin (g/dL)	N	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max,week56-60} (mg/L)	C _{max,week8-12} (mg/L)
Free aflibercept					
[2.5, 4.4)	532	83 (25.4%)	1.91 (40.5%)	0.134 (63.7%)	0.149 (57.5%)
[4.4, 4.6)	492	80 (23.8%)	1.97 (43.3%)	0.134 (55.6%)	0.15 (51%)
[4.6, 5.6]	662	80 (22.5%)	2.05 (58.9%)	0.146 (64.7%)	0.161 (60.1%)
Adjusted bound aflibercept					
[2.5, 4.4)	532	83 (25.4%)	20.6 (41%)	0.406 (36.9%)	0.722 (37.5%)
[4.4, 4.6)	492	80 (23.8%)	22.5 (42.8%)	0.426 (34.6%)	0.769 (36.2%)
[4.6, 5.6]	662	80 (22.5%)	23.4 (49.9%)	0.437 (38.8%)	0.791 (40.5%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max,week8-12} = maximum concentration from weeks 8 to 12, C_{max,week56-60} = maximum concentration from weeks 56 to 60, HDq16 = 8 mg aflibercept every 16 weeks following 3 initial monthly injections

Note: data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming HDq16 dosing for all participants.

[or] indicates that the respective limit is included in the interval;) indicates that the respective limit is not included in the interval

Source: Applicant's poppk report , Page 125 ([link](#)).

Participants with mild, moderate, or severe impairment were predicted to have elevated geometric mean for AUC_{tau} for adjusted bound aflibercept and free aflibercept. The summary of the post hoc predicted exposure are listed in Table 42, Table 43 and Table 44. The differences of AUC_{tau} between participants with normal renal function and participants with mild, moderate, or severe impairment in geometric mean of AUC_{tau} for adjusted bound aflibercept and free aflibercept are less than 40%, which is not clinically meaningful in this study.

Table 42. Summary of Post Hoc Model-Predicted Exposure Metrics for the 2q8 Dosing Regimen, Stratified by Renal Function in Participants from Studies PHOTON, PULSAR, and CANDELA

Renal function	eGFR (mL/min)	N	eGFR (mL/min)	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max, week56-60} (mg/L)	C _{max, week8-12} (mg/L)
Free aflibercept							
Normal	≥ 90	656	111 (15.7%)	90.1 (21.2%)	0.398 (55.3%)	0.0428 (54.9%)	0.0437 (54.2%)
Mild	60-89	732	75.2 (11.2%)	74.7 (22.9%)	0.488 (37.6%)	0.0436 (51.2%)	0.0452 (49.2%)
Moderate	30-59	271	49.2 (16.6%)	75.5 (23%)	0.511 (46.9%)	0.0427 (62.7%)	0.0448 (60.5%)
Severe*	< 30	27	20.1 (33.2%)	81.9 (20%)	0.47 (33.2%)	0.0408 (26.9%)	0.0424 (26.1%)
Adjusted bound aflibercept							
Normal	≥ 90	656	111 (15.7%)	90.1 (21.2%)	4.9 (45.6%)	0.132 (39.2%)	0.183 (37.9%)
Mild	60-89	732	75.2 (11.2%)	74.7 (22.9%)	6.29 (42.9%)	0.163 (38.8%)	0.229 (37.7%)
Moderate	30-59	271	49.2 (16.6%)	75.5 (23%)	6.78 (44.2%)	0.171 (37.5%)	0.242 (37.6%)
Severe*	< 30	27	20.1 (33.2%)	81.9 (20%)	5.86 (36.9%)	0.151 (30.9%)	0.214 (32.2%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max, week8-12} = maximum concentration from weeks 8 to 12, C_{max, week56-60} = maximum concentration from weeks 56 to 60, eGFR = estimated glomerular filtration, 2q8 = 2 mg aflibercept every 8 weeks following 5 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming 2q8 dosing for all participants. eGFR was calculated using the CKD-EPI equation.

* includes 21 participants with severe renal impairment (eGFR from 15 to < 30 mL/min) and 6 participants with renal failure (eGFR <15 mL/min)

Source: Applicant's poppk report, Page 131 ([link](#)).

Table 43. Summary of Post Hoc Model-Predicted Exposure Metrics for the HDq12 Dosing Regimen, Stratified by Renal Function in Participants from Studies PHOTON, PULSAR, and CANDELA

Renal function	eGFR (mL/min)	N	eGFR (mL/min)	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max, week56-60} (mg/L)	C _{max, week8-12} (mg/L)
Free aflibercept							
Normal	≥ 90	656	111 (15.7%)	90.1 (21.2%)	1.73 (59.9%)	0.139 (63.2%)	0.149 (59.7%)
Mild	60-89	732	75.2 (11.2%)	74.7 (22.9%)	2.13 (40.8%)	0.14 (58%)	0.158 (52%)
Moderate	30-59	271	49.2 (16.6%)	75.5 (23%)	2.22 (50.8%)	0.137 (71.7%)	0.158 (65.1%)
Severe*	< 30	27	20.1 (33.2%)	81.9 (20%)	2.03 (34.5%)	0.13 (29.7%)	0.147 (28.1%)
Adjusted bound aflibercept							
Normal	≥ 90	656	111 (15.7%)	90.1 (21.2%)	18.7 (45.1%)	0.398 (37.2%)	0.658 (37%)
Mild	60-89	732	75.2 (11.2%)	74.7 (22.9%)	24.1 (42.9%)	0.483 (37.5%)	0.82 (37.4%)
Moderate	30-59	271	49.2 (16.6%)	75.5 (23%)	26 (43.4%)	0.504 (34.6%)	0.863 (35%)
Severe*	< 30	27	20.1 (33.2%)	81.9 (20%)	22.6 (37.2%)	0.452 (29.4%)	0.768 (32.1%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max, week8-12} = maximum concentration from weeks 8 to 12, C_{max, week56-60} = maximum concentration from weeks 56 to 60, eGFR = estimated glomerular filtration, HDq12 = 8 mg aflibercept every 12 weeks following 3 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming HDq12 dosing for all participants. eGFR was calculated using the CKD-EPI equation.

* includes 21 participants with severe renal impairment (eGFR from 15 to < 30 mL/min) and 6 participants with renal failure (eGFR < 15 mL/min)

Source: Applicant's poppk report , Page 132 ([link](#)).

Table 44. Summary of Post Hoc Model-Predicted Exposure Metrics for the HDq16 Dosing Regimen, Stratified by Renal Function in Participants from Studies PHOTON, PULSAR, and CANDELA

Renal function	eGFR (mL/min)	N	eGFR (mL/min)	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max,week56-60} (mg/L)	C _{max,week8-12} (mg/L)
Free aflibercept							
Normal	≥ 90	656	111 (15.7%)	90.1 (21.2%)	1.72 (58.6%)	0.138 (63.2%)	0.149 (59.7%)
Mild	60-89	732	75.2 (11.2%)	74.7 (22.9%)	2.12 (40.8%)	0.14 (58.2%)	0.158 (52%)
Moderate	30-59	271	49.2 (16.6%)	75.5 (23%)	2.22 (50.6%)	0.137 (71.9%)	0.158 (65.1%)
Severe*	< 30	27	20.1 (33.2%)	81.9 (20%)	2.03 (34.5%)	0.129 (29.8%)	0.147 (28.1%)
Adjusted bound aflibercept							
Normal	≥ 90	656	111 (15.7%)	90.1 (21.2%)	18.7 (45.4%)	0.374 (36.3%)	0.658 (37%)
Mild	60-89	732	75.2 (11.2%)	74.7 (22.9%)	24.1 (43%)	0.452 (36.7%)	0.82 (37.4%)
Moderate	30-59	271	49.2 (16.6%)	75.5 (23%)	26 (43.5%)	0.47 (33.3%)	0.863 (35%)
Severe*	< 30	27	20.1 (33.2%)	81.9 (20%)	22.6 (37.2%)	0.423 (28.4%)	0.768 (32.1%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max,week8-12} = maximum concentration from weeks 8 to 12, C_{max,week56-60} = maximum concentration from weeks 56 to 60, eGFR = estimated glomerular filtration, HDq16 = 8 mg aflibercept every 16 weeks following 3 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming HDq16 dosing for all participants. eGFR was calculated using the CKD-EPI equation.

* includes 21 participants with severe renal impairment (eGFR from 15 to < 30 mL/min) and 6 participants with renal failure (eGFR <15 mL/min)

Source: Applicant's poppk report, Page 133 ([link](#)).

The geometric mean of AUC_{tau}, C_{max,week56-60}, and C_{max,week8-12} in the participants with mild hepatic impairment for free and adjusted bound aflibercept is similar to those of participants with normal hepatic function, shown in Table 45, Table 46 and Table 47. This suggested that mild hepatic impairment had no influence on aflibercept exposure metrics.

Table 45. Summary of Post Hoc Model-Predicted Exposure Metrics for the 2q8 Dosing Regimen, Stratified by Hepatic Function in Participants from Studies PHOTON, PULSAR, and CANDELA

Hepatic function	N	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max, week56-60} (mg/L)	C _{max, week8-12} (mg/L)
Free aflibercept					
Normal	1575	81.1 (24.1%)	0.457 (46.9%)	0.0429 (51.7%)	0.0444 (50.3%)
Mild*	85	78 (20.8%)	0.439 (36.2%)	0.0415 (38.8%)	0.0428 (37.6%)
Missing	26	81.2 (25.8%)	0.489 (55.8%)	0.0567 (121%)	0.0579 (119%)
Adjusted bound aflibercept					
Normal	1575	81.1 (24.1%)	5.83 (46.7%)	0.152 (40.6%)	0.213 (39.9%)
Mild*	85	78 (20.8%)	5.75 (35.6%)	0.153 (34.8%)	0.214 (34.5%)
Missing	26	81.2 (25.8%)	5.5 (36.5%)	0.149 (32.8%)	0.208 (33.6%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max, week8-12} = maximum concentration from weeks 8 to 12, C_{max, week56-60} = maximum concentration from weeks 56 to 60, 2q8 = 2 mg aflibercept every 8 weeks following 5 initial monthly injections

Note: data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming 2q8 dosing for all participants.

* includes 5 participants with moderate impairment

Source: Applicant's poppk report , Page 137 ([link](#)).

Table 46. Summary of Post Hoc Model-Predicted Exposure Metrics for the HDq12 Dosing Regimen, Stratified by Hepatic Function in Participants from Studies PHOTON, PULSAR, and CANDELA

Hepatic function	N	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max,week56-60} (mg/L)	C _{max,week8-12} (mg/L)
Free aflibercept					
Normal	1575	81.1 (24.1%)	1.99 (50.6%)	0.138 (59.1%)	0.154 (54.4%)
Mild*	85	78 (20.8%)	1.9 (38.4%)	0.133 (42.2%)	0.147 (39.3%)
Missing	26	81.2 (25.8%)	2.16 (63.3%)	0.19 (136%)	0.203 (127%)
Adjusted bound aflibercept					
Normal	1575	81.1 (24.1%)	22.3 (46.4%)	0.453 (38.5%)	0.763 (38.9%)
Mild*	85	78 (20.8%)	22.1 (35.5%)	0.459 (34.3%)	0.771 (33.8%)
Missing	26	81.2 (25.8%)	20.8 (35.7%)	0.442 (30.2%)	0.736 (31.9%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max,week8-12} = maximum concentration from weeks 8 to 12, C_{max,week56-60} = maximum concentration from weeks 56 to 60, HDq12 = 8 mg aflibercept every 12 weeks following 3 initial monthly injections

Note: data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming HDq12 dosing for all participants.

* includes 5 participants with moderate impairment

Source: Applicant's poppk report , Page 138([link](#)).

Table 47. Summary of Post Hoc Model-Predicted Exposure Metrics for the HDq16 Dosing Regimen, Stratified by Hepatic Function in Participants from Studies PHOTON, PULSAR, and CANDELA

Hepatic function	N	Body weight (kg)	AUCtau (mg x day/L)	C _{max,week56-60} (mg/L)	C _{max,week8-12} (mg/L)
Free aflibercept					
Normal	1575	81.1 (24.1%)	1.98 (50%)	0.138 (59.2%)	0.154 (54.4%)
Mild*	85	78 (20.8%)	1.9 (38.4%)	0.133 (42.3%)	0.147 (39.3%)
Missing	26	81.2 (25.8%)	2.16 (63.3%)	0.189 (136%)	0.203 (127%)
Adjusted bound aflibercept					
Normal	1575	81.1 (24.1%)	22.3 (46.5%)	0.424 (37.4%)	0.763 (38.9%)
Mild*	85	78 (20.8%)	22.1 (35.5%)	0.432 (34.6%)	0.771 (33.8%)
Missing	26	81.2 (25.8%)	20.8 (35.7%)	0.418 (29.8%)	0.736 (31.9%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max,week8-12} = maximum concentration from weeks 8 to 12, C_{max,week56-60} = maximum concentration from weeks 56 to 60, HDq16 = 8 mg aflibercept every 16 weeks following 3 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming HDq16 dosing for all participants.

* includes 5 participants with moderate impairment

Source: Applicant's poppk report, Page 139([link](#)).

The geometric mean of AUCtau in the different racial groups, and for Japanese versus non-Japanese participants were generally in the range of 25% difference for free and adjusted bound aflibercept, shown in Table 51, Table 52 and Table 53. Participants identified as black have geometric mean exposure metrics of free aflibercept within -3% and +9% of those identified as white and up to 23% lower for adjusted bound aflibercept, shown in Table 48, Table 49 and Table 50. Therefore, there is no clinically significant difference in races.

Table 48. Summary of Post Hoc Model-Predicted Exposure Metrics for the 2q8 Dosing Regimen, Stratified by Racial Group in Participants from Studies PHOTON, PULSAR, and CANDELA

Racial group	N	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max,week56-60} (mg/L)	C _{max,week8-12} (mg/L)
Free aflibercept					
White	1325	83.4 (22.9%)	0.445 (49.2%)	0.0417 (53%)	0.0432 (51.6%)
Black	64	91.1 (19.2%)	0.429 (46.5%)	0.047 (95.8%)	0.0479 (94.3%)
Asian	264	66 (20.5%)	0.521 (33.9%)	0.0486 (45.2%)	0.0502 (43.4%)
Other	33	91.2 (20.7%)	0.444 (36.1%)	0.045 (34.3%)	0.0461 (33.3%)
Adjusted bound aflibercept					
White	1325	83.4 (22.9%)	5.87 (44.6%)	0.152 (39.2%)	0.213 (38.7%)
Black	64	91.1 (19.2%)	4.45 (35.6%)	0.121 (32.2%)	0.169 (32.5%)
Asian	264	66 (20.5%)	5.98 (52.2%)	0.16 (43.8%)	0.224 (42.4%)
Other	33	91.2 (20.7%)	5.24 (41.8%)	0.144 (41.6%)	0.2 (40.6%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max,week8-12} = maximum concentration from weeks 8 to 12, C_{max,week56-60} = maximum concentration from weeks 56 to 60, 2q8 = 2 mg aflibercept every 8 weeks following 5 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming 2q8 dosing for all participants.

Source: Applicant's poppk report, Page 148([link](#)).

Table 49. Summary of Post Hoc Model-Predicted Exposure Metrics for the HDq12 Dosing Regimen, Stratified by Racial Group in Participants from Studies PHOTON, PULSAR, and CANDELA

Racial group	N	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max,week56-60} (mg/L)	C _{max,week8-12} (mg/L)
Free aflibercept					
White	1325	83.4 (22.9%)	1.93 (53.1%)	0.134 (60.7%)	0.149 (56%)
Black	64	91.1 (19.2%)	1.87 (52.4%)	0.153 (110%)	0.164 (103%)
Asian	264	66 (20.5%)	2.29 (36.3%)	0.158 (51%)	0.176 (45.9%)
Other	33	91.2 (20.7%)	1.94 (37.8%)	0.146 (37.3%)	0.158 (35.1%)
Adjusted bound aflibercept					
White	1325	83.4 (22.9%)	22.5 (44%)	0.453 (37.2%)	0.765 (37.3%)
Black	64	91.1 (19.2%)	16.9 (34.6%)	0.365 (29.5%)	0.604 (30.6%)
Asian	264	66 (20.5%)	22.8 (53.4%)	0.476 (42%)	0.797 (43.4%)
Other	33	91.2 (20.7%)	20 (41.1%)	0.436 (41%)	0.716 (38.8%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max,week8-12} = maximum concentration from weeks 8 to 12, C_{max,week56-60} = maximum concentration from weeks 56 to 60, HDq12 = 8 mg aflibercept every 12 weeks following 3 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming HDq12 dosing for all participants.

Source: Applicant's poppk report , Page 149([link](#)).

Table 50. Summary of Post Hoc Model-Predicted Exposure Metrics for the HDq16 Dosing Regimen, Stratified by Racial Group in Participants from Studies PHOTON, PULSAR, and CANDELA

Racial group	N	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max,week56-60} (mg/L)	C _{max,week8-12} (mg/L)
Free aflibercept					
White	1325	83.4 (22.9%)	1.93 (52.5%)	0.134 (60.8%)	0.149 (56%)
Black	64	91.1 (19.2%)	1.86 (52.4%)	0.153 (110%)	0.164 (103%)
Asian	264	66 (20.5%)	2.28 (36.3%)	0.158 (51.2%)	0.176 (45.9%)
Other	33	91.2 (20.7%)	1.93 (37.8%)	0.145 (37.4%)	0.158 (35.1%)
Adjusted bound aflibercept					
White	1325	83.4 (22.9%)	22.5 (44.2%)	0.423 (36.4%)	0.765 (37.3%)
Black	64	91.1 (19.2%)	16.9 (34.6%)	0.345 (28.8%)	0.604 (30.6%)
Asian	264	66 (20.5%)	22.8 (53.4%)	0.449 (39.7%)	0.797 (43.4%)
Other	33	91.2 (20.7%)	20 (41.2%)	0.413 (41.8%)	0.716 (38.8%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max,week8-12} = maximum concentration from weeks 8 to 12, C_{max,week56-60} = maximum concentration from weeks 56 to 60, HDq16 = 8 mg aflibercept every 16 weeks following 3 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming HDq16 dosing for all participants.

Source: Applicant's poppk report, Page 150([link](#)).

Table 51. Summary of Post Hoc Model-Predicted Exposure Metrics for the 2q8 Dosing Regimen, Stratified by Japanese Origin in Participants from Studies PHOTON, PULSAR, and CANDELA

Japanese origin	N	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max,week56-60} (mg/L)	C _{max,week8-12} (mg/L)
Free aflibercept					
No	1515	82.8 (23.1%)	0.447 (47.8%)	0.0422 (54.7%)	0.0437 (53.3%)
Yes	171	64.6 (20.3%)	0.538 (34.5%)	0.0506 (48.7%)	0.0522 (46.8%)
Adjusted bound aflibercept					
No	1515	82.8 (23.1%)	5.8 (44%)	0.151 (38.7%)	0.212 (38.3%)
Yes	171	64.6 (20.3%)	5.98 (60.2%)	0.16 (50.1%)	0.225 (48.1%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max,week8-12} = maximum concentration from weeks 8 to 12, C_{max,week56-60} = maximum concentration from weeks 56 to 60, 2q8 = 2 mg aflibercept every 8 weeks following 5 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming 2q8 dosing for all participants.

Source: Applicant's poppk report, Page 151([link](#)).

Table 52. Summary of Post Hoc Model-Predicted Exposure Metrics for the HDq12 Dosing Regimen, Stratified by Japanese Origin in Participants from Studies PHOTON, PULSAR, and CANDELA

Japanese origin	N	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max, week56-60} (mg/L)	C _{max, week8-12} (mg/L)
Free aflibercept					
No	1515	82.8 (23.1%)	1.94 (51.6%)	0.136 (62.6%)	0.151 (57.7%)
Yes	171	64.6 (20.3%)	2.37 (37.3%)	0.166 (55.1%)	0.183 (49.4%)
Adjusted bound aflibercept					
No	1515	82.8 (23.1%)	22.2 (43.5%)	0.45 (36.7%)	0.759 (37%)
Yes	171	64.6 (20.3%)	22.7 (61.8%)	0.477 (48.1%)	0.796 (49.5%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max, week8-12} = maximum concentration from weeks 8 to 12, C_{max, week56-60} = maximum concentration from weeks 56 to 60, HDq12 = 8 mg aflibercept every 12 weeks following 3 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming HDq12 dosing for all participants.

Source: Applicant's poppk report, Page 151 ([link](#)).

Table 53. Summary of Post Hoc Model-Predicted Exposure Metrics for the HDq16 Dosing Regimen, Stratified by Japanese Origin in Participants from Studies PHOTON, PULSAR, and CANDELA

Japanese origin	N	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max, week56-60} (mg/L)	C _{max, week8-12} (mg/L)
Free aflibercept					
No	1515	82.8 (23.1%)	1.94 (51.1%)	0.136 (62.7%)	0.151 (57.7%)
Yes	171	64.6 (20.3%)	2.36 (37.3%)	0.165 (55.2%)	0.183 (49.4%)
Adjusted bound aflibercept					
No	1515	82.8 (23.1%)	22.2 (43.7%)	0.421 (35.9%)	0.759 (37%)
Yes	171	64.6 (20.3%)	22.7 (61.8%)	0.45 (45.2%)	0.796 (49.5%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max, week8-12} = maximum concentration from weeks 8 to 12, C_{max, week56-60} = maximum concentration from weeks 56 to 60, HDq16 = 8 mg aflibercept every 16 weeks following 3 initial monthly injections

Note: data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming HDq16 dosing for all participants.

Source: Applicant's poppk report, Page 152 ([link](#)).

Differences of geometric mean of AUC_{tau}, C_{max, week56-60}, and C_{max, week8-12} of free aflibercept between DME and nAMD are less 25%, while those of adjusted bound aflibercept are about 20% to 25%, shown in Table 54, Table 55 and Table 56.

Table 54. Summary of Post Hoc Model-Predicted Exposure Metrics for the 2q8 Dosing Regimen, Stratified by Disease Population in Participants from Studies PHOTON, PULSAR, and CANDELA

Population	N	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max, week56-60} (mg/L)	C _{max, week8-12} (mg/L)
Free aflibercept					
nAMD	1038	77.2 (22.7%)	0.471 (50.5%)	0.0411 (56.1%)	0.0429 (54.4%)
DME	648	86.9 (23.8%)	0.434 (37.4%)	0.0462 (51.1%)	0.0472 (50%)
Adjusted bound aflibercept					
nAMD	1038	77.2 (22.7%)	6.41 (44.8%)	0.164 (39.6%)	0.231 (38.3%)
DME	648	86.9 (23.8%)	4.87 (41%)	0.132 (36.2%)	0.184 (36.7%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max, week8-12} = maximum concentration from weeks 8 to 12, C_{max, week56-60} = maximum concentration from weeks 56 to 60, 2q8 = 2 mg aflibercept every 8 weeks following 5 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming 2q8 dosing for all participants.

Source: Applicant's poppk report , Page 156 ([link](#)).

Table 55. Summary of Post Hoc Model-Predicted Exposure Metrics for the HDq12 Dosing Regimen, Stratified by Disease Population in Participants from Studies PHOTON, PULSAR, and CANDELA

Population	N	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max, week56-60} (mg/L)	C _{max, week8-12} (mg/L)
Free aflibercept					
nAMD	1038	77.2 (22.7%)	2.05 (54.9%)	0.132 (64%)	0.15 (58.5%)
DME	648	86.9 (23.8%)	1.89 (39.7%)	0.15 (58.4%)	0.161 (54.6%)
Adjusted bound aflibercept					
nAMD	1038	77.2 (22.7%)	24.6 (44.1%)	0.487 (37.7%)	0.828 (37%)
DME	648	86.9 (23.8%)	18.5 (41.4%)	0.399 (34.8%)	0.658 (36.3%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max, week8-12} = maximum concentration from weeks 8 to 12, C_{max, week56-60} = maximum concentration from weeks 56 to 60, HDq12 = 8 mg aflibercept every 12 weeks following 3 initial monthly injections

Note: data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming HDq12 dosing for all participants.

Source: Applicant's poppk report , Page 156 ([link](#)).

Table 56. Summary of Post Hoc Model-Predicted Exposure Metrics for the HDq16 Dosing Regimen, Stratified by Disease Population in Participants from Studies PHOTON, PULSAR, and CANDELA

Population	N	Body weight (kg)	AUC _{tau} (mg x day/L)	C _{max, week56-60} (mg/L)	C _{max, week8-12} (mg/L)
Free aflibercept					
nAMD	1038	77.2 (22.7%)	2.04 (54.2%)	0.132 (64.2%)	0.15 (58.5%)
DME	648	86.9 (23.8%)	1.89 (39.7%)	0.15 (58.5%)	0.161 (54.6%)
Adjusted bound aflibercept					
nAMD	1038	77.2 (22.7%)	24.6 (44.3%)	0.454 (36.7%)	0.828 (37%)
DME	648	86.9 (23.8%)	18.5 (41.4%)	0.376 (34.1%)	0.658 (36.3%)

AUC_{tau} = area under the concentration curve from time 0 to end of dosing period, CV = coefficient of variation, C_{max, week8-12} = maximum concentration from weeks 8 to 12, C_{max, week56-60} = maximum concentration from weeks 56 to 60, HDq16 = 8 mg aflibercept every 16 weeks following 3 initial monthly injections

Note: Data are presented as mean (CV%). Exposures were simulated using post hoc PK estimates of participants from Studies PHOTON, PULSAR, and CANDELA assuming HDq16 dosing for all participants.

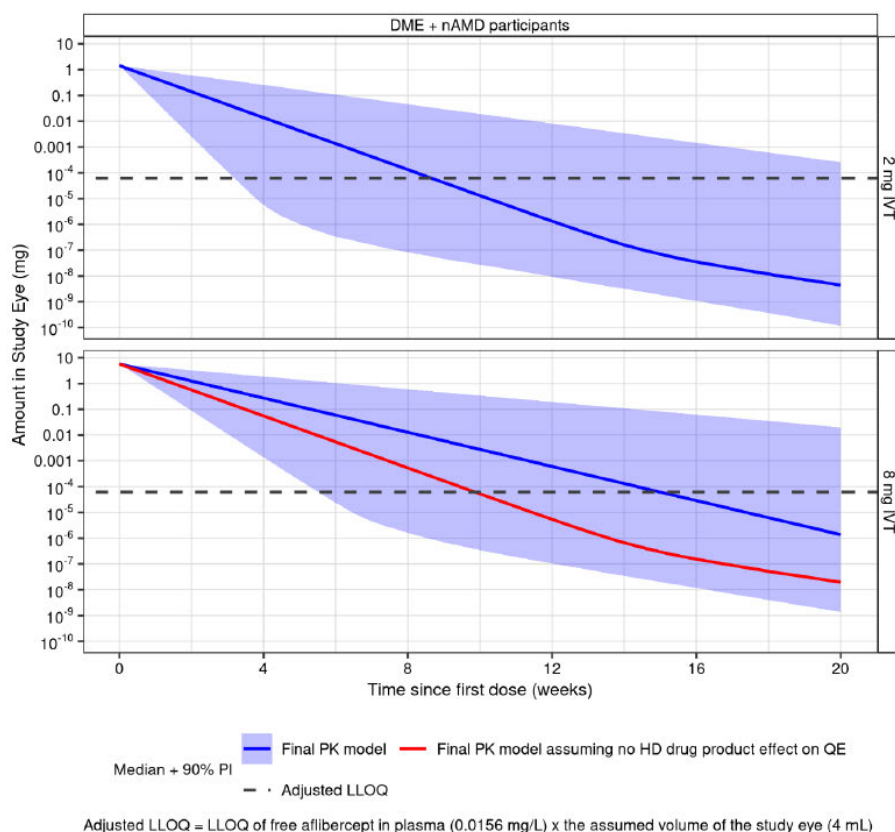
Source: Applicant's poppk report , Page 157 ([link](#)).

Reviewer's comment:

The PopPK model reasonably well described the aflibercept plasma concentration. Sponsor has conducted exploratory analyses and concluded the slower ocular clearance and longer duration of free aflibercept ocular exposure of HD aflibercept contribute to the drug effect of HD aflibercept (Figure 25). But as there is no observed ocular concentration of aflibercept to confirm the prediction, such interpretation should be treated with caution. Moreover, in order to converge the final model, some of the model parameter estimates in the final model were fixed based on previous models. Although M3 methods was used, the percentage of BLQ data is still very high (>60%). Furthermore, although the final PopPK model was able to predict the adjusted bound concentrations in the 2 mg cohort in Study 1905 (nAMD patients) reasonably well, the model largely under predicted the adjusted bound concentrations of the 2 mg cohort in Study 20968 (nAMD patients).⁴ Therefore, cautious interpretation of the PopPK model, simulations based on the final PopPK model, and exposure-response analyses are needed given above limitations.

Figure 25. Model-predicted amounts of aflibercept exposures after a single IVT injection, stratified by dosing regimen in combined participants with nAMD and DME

⁴ Source: Applicant's poppk report , Page 167 ([link](#)).



DME = diabetic macular edema, HD = aflibercept 8 mg, IVT = intravitreal, nAMD = neurovascular age-related macular degeneration, PI = prediction interval, PK = pharmacokinetics, QE = inter-compartmental clearance between ocular compartment and central compartment of free aflibercept

Adjusted LLOQ (0.0624 µg), set as the LLOQ of free aflibercept in plasma (that is, 0.0156 mg/L) times the assumed volume of the study eye compartment in the PK model (that is, 4 mL). Since the concentrations of (free or bound) aflibercept were not measured in the study eye in the clinical studies included in the Population PK analysis dataset, this target was selected arbitrarily on the basis of the LLOQ in plasma and was used as reference for comparison across dosing regimens and to assess the effect of the effect of HD aflibercept on QE.

Source: Module 5.3.3.5 Population PK Simulation Report Synopsis

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LEI HE
04/21/2023 02:51:59 PM

HEZHEN WANG
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YOUWEI N BI
04/21/2023 10:18:59 PM

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04/22/2023 09:47:06 PM