# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761355Orig1s000

# SUMMARY REVIEW

# Clinical, Team Leader, and Division Director Review of BLA 761355

| | |
|---|---|
| **Application Type** | Resubmission of BLA |
| **Application Number** | BLA 761355 (IND 12462) |
| **Priority or Standard** | Original submission received a priority review based on use of Priority Review Voucher for Medical Counter Measures |
| **Original Submit Date** | December 27, 2022 – 1st Action (CR) June 27, 2023 |
| **Resubmission Date** | July 3, 2023 |
| **PDUFA Goal Date** | January 3, 2024 |
| **Division/Office** | Division of Ophthalmology/Office of Specialty Medicine |
| **Review Completion Date** | August 18, 2023 |
| **Established/Proper Name** | Aflibercept |
| **(Proposed) Trade Name** | Eylea HD |
| **Applicant** | Regeneron Pharmaceuticals, Inc. |
| **Dosage Form** | Intravitreal Injection |
| **Product concentration** | Aflibercept 114.3 mg/mL |
| **Dosing Regimen** | 8 mg monthly intravitreal injection (delivered as 0.07mL) x 3 followed by q8-16 weeks for nAMD and DME. 8 mg monthly intravitreal injection (delivered as 0.07mL) x 3 followed by q8-12 weeks for DR. |
| **Proposed Indications** | Neovascular Age Related Macular Degeneration (nAMD), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) |
| **Recommendation on Regulatory Action** | Approval |

## Glossary

| | |
|---|---|
| AC | advisory committee |
| AE | adverse event |
| AMD | age-related macular degeneration |
| AR | adverse reaction |
| BLA | biologics license application |
| BPCA | Best Pharmaceuticals for Children Act |
| BRF | Benefit Risk Framework |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| CRF | case report form |
| CRO | contract research organization |
| CSR | clinical study report |
| DMC | data monitoring committee |

| | |
|---|---|
| DME | diabetic macular edema |
| DR | diabetic retinopathy |
| eCTD | electronic common technical document |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GCP | good clinical practice |
| ICH | International Council for Harmonization |
| IND | Investigational New Drug Application |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| nAMD | neovascular age-related macular degeneration |
| NDA | new drug application |
| NME | new molecular entity |
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PD | pharmacodynamics |
| PI | prescribing information or package insert |
| PK | pharmacokinetics |
| PMC | post-marketing commitment |
| PMR | post-marketing requirement |
| PP | per protocol |
| PPI | patient package insert |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGE | special government employee |
| SOC | standard of care |
| TEAE | treatment emergent adverse event |

# 1. Executive Summary

## 1.1. Product Introduction

Aflibercept is an inhibitor of vascular endothelial growth factor (VEGF). It is a recombinant fusion protein consisting of extracellular domains 2 and 3 of human VEGF receptors, VEGFR-1 and VEGFR-2, fused to the Fc portion of human immunoglobulin VEGF is overexpressed in several retinal diseases with neovascularization.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

In three adequate and well controlled trials, 8 mg of aflibercept administered intravitreally every 8 to 16 weeks was non-inferior to 2 mg administered every 8 weeks for the treatment of nAMD and DME. Eight (8) mg of aflibercept administered intravitreally every 8-12 weeks was non-inferior to 2 mg aflibercept administered every 8 weeks for the treatment of DR.

## 1.3. Benefit-Risk Integrated Assessment

The benefits of aflibercept 8 mg administered intravitreally outweigh the risk because studies PHOTON (VGFTe-HD-DME-1934), CANDELA (VGFTe[HD]-AMD-1905 and PULSAR (20968), demonstrated the non-inferiority (margin of 4 letters) of aflibercept 8 mg dosed every 8-12 weeks to aflibercept 2 mg dosed every 8 weeks in the treatment of nAMD, DME and DR. Studies CANDELA (VGFTe[HD]-AMD-1905 and PULSAR (20968), demonstrated the non-inferiority (margin of 4 letters) of aflibercept 8 mg dosed every 16 weeks to aflibercept 2 mg dosed every 8 weeks in the treatment of nAMD, and DME. The most common ocular adverse events after treatment with aflibercept 8 mg included cataract, conjunctival hemorrhage, intraocular pressure increased, ocular discomfort/eye pain/eye irritation, vision blurred, vitreous floaters, vitreous detachment, corneal epithelium defect, and retinal hemorrhage. Serious adverse events were reported rarely. There is clinical safety and efficacy to support the approval of the application. A complete response letter was issued during the first review cycle because one of the manufacturing facilities (b) (4) was found to be noncompliant with current Good Manufacturing Practices (cGMPs). With the resubmission of the application, there has been satisfactory resolution of the observations at (b) (4). All manufacturing facilities are now considered to be compliant with cGMPs.

Benefit-Risk Dimensions

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Vision loss in nAMD results from the abnormal growth and leakage of blood vessels in the macula.<br>• DR is a microangiopathy that occurs in both Type 1 and Type 2 DM. The pathology includes upregulation of vascular endothelial growth factor (VEGF) and other angiogenic, inflammatory and vascular permeability factors.<br>• The most common cause of vision loss from DR is DME, which can occur at any stage of DR and is characterized by retinal edema and retinal thickening. | IVT-administered anti-VEGF therapies, like aflibercept, inhibit neovascular vessel growth and leakage in the retina, and they are currently the standard of care for patients with nAMD, and serve as an alternative treatment in DME and DR when blood sugar control failures. |
| Current Treatment Options | • Lucentis, Eylea, Vabysmo and Beovu are approved for the treatment of AMD and DME. Lucentis, and Eylea are approved for the treatment of DR. Multiple corticosteroids are approved for the treatment of DME. Avastin is prescribed off-label for the treatment of AMD, DME and DR. | Approval of an alternative dosing regimen will provide options for treating individuals with nAMD, DME and DR. |
| Benefit | • Treatment of AMD, DME and DM can prevent vision loss. | 8 mg of aflibercept administered intravitreally every 8 to 16 weeks was non-inferior to 2 mg administered every 8 weeks for the treatment of nAMD and DME. Eight (8) mg of aflibercept administered intravitreally every 8-12 weeks was non inferior to 2 mg aflibercept administered every 8 weeks for the treatment of DR. |
| Risk and Risk Management | • The most common ocular adverse events after treatment with aflibercept 8 mg were cataract, conjunctival hemorrhage, intraocular pressure increased, ocular discomfort/eye pain/eye irritation, vision blurred, vitreous floaters, vitreous detachment, corneal epithelium defect, and retinal hemorrhage. Serious adverse events were reported rarely. | Routine post market monitoring and reporting of all adverse events can potentially identify rare adverse reactions not observed in clinical trials. |

## 2. Patient Experience Data Relevant to this Application (check all that apply)

| | | | | |
|---|---|---|---|---|
| ☒ | The patient experience data that was submitted as part of the application include: | | | Section where discussed, if applicable |
| | ☒ | Clinical outcome assessment (COA) data, such as | | |
| | | ☐ | Patient reported outcome (PRO) | |
| | | ☒ | Observer reported outcome (ObsRO) | Section 6 AMD and DME |
| | | ☒ | Clinician reported outcome (ClinRO) | Section 6 DR |
| | | ☐ | Performance outcome (PerfO) | |
| | ☐ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | |
| | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | ☐ | Observational survey studies designed to capture patient experience data | | |
| | ☐ | Natural history studies | | |
| | ☐ | Patient preference studies (e.g., submitted studies or scientific publications) | | |
| | ☐ | Other: (Please specify) | | |
| ☐ | Patient experience data that were not submitted in the application, but were considered in this review: | | | |
| | | ☐ | Input informed from participation in meetings with patient stakeholders | |
| | | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | |
| | | ☐ | Observational survey studies designed to capture patient experience data | |
| | | ☐ | Other: (Please specify) | |
| ☐ | Patient experience data was not submitted as part of this application. | | | |

# 3. Therapeutic Context

## 3.1. Analysis of Condition

Vision loss in nAMD results from the abnormal growth and leakage of blood vessels in the macula. DR is a microangiopathy that occurs in both Type 1 and Type 2 DM. The pathology of DR includes upregulation of vascular endothelial growth factor (VEGF) and other angiogenic, inflammatory and vascular permeability factors. The most common cause of vision loss from DR is DME, which can occur at any stage of DR and is characterized by retinal edema and retinal thickening.

## 3.2. Analysis of Current Treatment Options

Lucentis (ranibizumab injection), Eylea (aflibercept), Vabysmo (faricimab-svoa) and Beovu (brolucizumab-dbll) are approved for the treatment of AMD and DME. Lucentis and Eylea are approved for the treatment of DR. Multiple corticosteroids are approved for the treatment of DME. Avastin is prescribed off-label for the treatment of AMD, DME and DR.

## 3.3. U.S. Regulatory Actions and Marketing History

Aflibercept 2 mg is an approved product in the US for the following indications:

| | |
|---|---|
| Original BLA 125387: Treatment of neovascular (wet) AMD | 11/18/2011 |
| S004: Treatment of macular edema secondary to CRVO | 9/21/2012 |
| S037: Treatment of diabetic macular edema DME | 7/29/2014 |
| S043: Treatment of macular edema secondary to BRVO | 10/6/2014 |
| S048: Treatment of diabetic retinopathy in patients with DME | 3/25/2015 |
| S061: Treatment of diabetic retinopathy | 5/13/2019 |
| S075: Treatment of retinopathy of prematurity | 2/8/2023 |

## 3.4. Summary of Pre-submission/Submission Regulatory Activity

- The Agency confirmed that for a "rearrangement of dose" (a higher amount of drug with less frequent dosing), a single non-inferiority adequate and well controlled study for nAMD (PULSAR) and a single non-inferiority adequate and well controlled study for DME (PHOTON) investigating extended dosing intervals (e.g., Q12W or Q16W) for HD aflibercept compared to the approved EYLEA 2mg regimen (Q8W) could serve as acceptable clinical support for registration of these indications. [FDA Meeting Minutes Reference ID: 4387341.]
- At a Type C meeting on 29 November 2021, Agency agreed that it is acceptable to submit a new, original BLA to register HD aflibercept in the indications of DME and nAMD [Reference ID 4901050].
- A Type B, Pre-BLA meeting [Reference ID: 5047962] was held with FDA on 26 September 2022 wherein the Agency:
  - Reconfirmed that the submission of an original BLA was acceptable. The Agency also agreed that the cross-referencing strategy proposed by the Sponsor to EYLEA BLA (125387) is acceptable.
  - Indicated that the PHOTON and PULSAR study designs and statistical analysis plans (SAPs), as proposed and conducted, are sufficient for filing a new BLA for nAMD and DME indications.
  - Confirmed that the PHOTON study results are sufficient for review of a submission filing for a broad DR indication, with the FDA requiring that the Sponsor consider a 10% non-inferiority margin for the endpoint of proportion of patients with a ≥2 step improvement in Diabetic Retinopathy Severity Scale (DRSS) Score.
  - The Agency confirmed that the draft Table of Contents provided in Regeneron's meeting briefing package appears reasonable. Additionally, the Agency agreed that since PHOTON and PULSAR are single studies for separate indications, the requirement for a pooled analyses for integrated efficacy and safety is waived.
  - The Agency confirmed that a 'vial-only' presentation would be regulated solely as a biological product, whereas the 'vial kit' presentation (consisting of syringe, filter needle and injection needle) is a convenience kit that will be regulated as a combination product.

## 3.5. Foreign Regulatory Actions and Marketing History

Eylea 2 mg is marketed for a variety of indications throughout the world. Eylea HD 8 mg is not approved in any jurisdiction.

# 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

## 4.1. Office of Scientific Investigations (OSI)

From the Clinical Inspection Summary: The clinical sites of Drs. Ernest, Win, and Sarrafizadeh were inspected in support of this BLA. Based on the results of these inspections, Protocols 1934 and 20968 appears to have been conducted adequately and the data generated by these sites appear acceptable in support of the proposed indication.

## 4.2. Product Quality

This marketing application provides support for regulatory review and approval of HD (8 mg) aflibercept, a drug product able to deliver a higher milligram dose of aflibercept (8 mg; delivered as a 0.07 mL intravitreal [IVT] injection of 114.3 mg/mL) for the treatment of adult patients with nAMD, diabetic macular edema (DME), and diabetic retinopathy (DR). The drug product includes two presentations, a 'vial-only' presentation consisting of a vial (primary container in a carton) and a 'vial kit' - a convenience kit consisting of a vial co-packaged in a carton with a syringe (510(k) cleared (b) (4), filter needle (Class I exempt device) and injection needle (510(k) cleared, (b) (4).

**Proposed Formulation for Eylea HD**

| Component | Function | Quality Standard | Concentration | Content per Vial (mg)[a] | Content per 0.07 mL Withdrawable Volume (mg) |
|---|---|---|---|---|---|
| Aflibercept | Active ingredient | Regeneron specification | 114.3 mg/mL | (b) (4) | 8.00 |
| (b) (4) arginine (b) (4) hydrochloride | (b) (4) | USP, Ph. Eur., JP | (b) (4) | | 0.737 |
| (b) (4) histidine | | USP, Ph. Eur., JP | (b) (4) | | 0.040 |
| L-histidine (b) (4) hydrochloride monohydrate | | Ph. Eur., JP | (b) (4) | | 0.093 |
| Sucrose | | NF, Ph. Eur., JP | (b) (4) % (w/v) | | 3.50 |
| Polysorbate 20 | | NF, Ph. Eur., JPE | (b) (4) % (w/v) | | 0.021 |
| Water for Injection | | USP, Ph. Eur., JP | QS | | QS |

(mg)[a] Calculations are based on a target fill volume of (b) (4) mL/vial. JP, Japanese Pharmacopeia; JPE, Japanese Pharmaceutical Excipients; NF, National Formulary; Ph. Eur., European; USP, United States Pharmacopeia; w/v, weight by volume.

## Comparison between Eylea HD and Eylea

| Ingredient | Function | Eylea Drug Product Concentration (mg/mL) | Eylea HD Drug Product Concentration (mg/mL) |
|---|---|---|---|
| Aflibercept | Active Ingredient | 40 | 114.3 |
| [redacted] | [redacted] | | |
| [redacted] | [redacted] | | |
| [redacted] | [redacted] | | |
| [redacted] | [redacted] | [redacted] | |
| [redacted] | [redacted] | | |
| [redacted] | [redacted] | [redacted] | |
| [redacted] | [redacted] | [redacted] | |
| [redacted] | [redacted] | | |
| Water for Injection (WFI) | [redacted] | Quantity sufficient | |

[redacted]

USP=United States Pharmacopeia, BP=British Pharmacopeia, Ph. Eur.=European Pharmacopeia, JP=Japanese Pharmacopeia, JPE=Japanese Pharmaceutical Excipients, NF=National Formulary.

## Specifications for Drug Product

| Test | Method | Acceptance Criteria | |
|---|---|---|---|
| | | Release | End of Shelf-Life |
| Physical form/condition | Visual inspection USP <790><br>Ph. Eur. *2.9.20* JP *<6.06>* | Liquid essentially free from visible particulates | Same as release |
| Clarity | Comparison to reference suspension USP <855><br>Ph. Eur. *2.2.1* JP *<2.61>* | Not more turbid than reference suspension IV | Same as release |
| Color | Comparison to reference solutions USP <1061><br>Ph. Eur. *2.2.2* JP*<2.65>* | Not more colored than reference solution [redacted] | Same as release |
| pH | Potentiometry USP <791><br>Ph. Eur. *2.2.3* JP *<2.54>* | [redacted] | Same as release |
| Identity by Dot Blot | Dot blot | Conforms to standard | Not tested |
| Total protein content ($A_{280}$) | UV spectrophotometry | [redacted] mg/mL | Same as release |
| Potency | Cell based bioassay | [redacted] % of reference standard | Same as release |
| Purity by reduced CE- SDS<br>% Purity<br>% R1<br>% LMW Less R1 | Capillary electrophoresis- sodium dodecyl sulfate | [redacted] | |
| Purity by non-reduced CE-SDS | | | |
| Purity by SE-UPLC<br>% Purity<br>% Aggregate | Liquid chromatography | | |

| Test | Method | Acceptance Criteria | |
|---|---|---|---|
| | | Release | End of Shelf-Life |
| Charge variant analysis by iCIEF<br><br>% Region 1<br>% Region 2<br>% Region 3 | Isoelectric focusing | The test article electropherogram should be qualitatively similar to the reference standard electropherogram in terms of intensity, number and pattern of peaks.<br>(b) (4) % | Same as release |
| (b) (4) content | (b) (4) HPLC/UV | (b) (4) | |
| Endotoxin content | KTA USP <85><br>Ph. Eur. *2.6.14* JP *<4.01>* | ≤ 0.2 EU/mL | Not tested |
| Sterility (filled container) | Membrane filtration USP <71><br>Ph. Eur. *2.6.1* JP *<4.06>* | Meets USP, Ph. Eur., and JP requirements | Not tested |
| Particulate matter content<br>Particles ≥ 10µm<br>Particles ≥ 25µm<br>Particles ≥ 50µm | Light Obscuration<br>USP <788> and <789><br>Ph. Eur. *2.9.19*<br>JP *<6.07>* | ≤ (b) (4) particles/mL<br>≤ articles/mL<br>≤ articles/mL | Same as release |
| Volume in container | Volume in container USP <697><br>Ph. Eur. *2.9.17*<br>JP *<6.05>* | 0.07 mL minimum withdrawable content | Not tested |
| Container Closure Integrity (CCI) | Mass extraction USP <1270> | Not tested | No leak detected |

$A_{280}$, absorbance at 280 nm; EU, endotoxin units; HMW, high molecular weight; HPLC, high performance liquid chromatography; iCIEF, imaged capillary isoelectric focusing; JP, Japanese Pharmacopeia; KTA, kinetic turbidimetric assay; LMW, low molecular weight; CE-SDS, capillary electrophoresis-sodium dodecyl sulfate; SE-UPLC, size-exclusion ultra-performance liquid chromatography; UV, ultraviolet

**Reviewer's Comments:** *Acceptable.*

**Summary of Quality Assessments- Office of Biotechnology Products**

Aflibercept (Eylea high dose [HD]) is manufactured from a (b) (4), for the same presentations (single-dose vial and single-dose vial kit) and route of administration (intravitreal injection) for which Eylea is currently approved. The Eylea HD product is a sterile aqueous buffered solution, pH 5.8, containing 114.3 mg/mL aflibercept, (b) (4) arginine (b) (4) hydrochloride, (b) (4) -histidine, (b) (4) % (w/v) sucrose, and (b) (4) % (w/v) polysorbate 20. The DP is filled into a (b) (4) glass vial with an (b) (4) stopper, and sealed with an aluminum seal cap. Each vial has a 0.07 mL withdrawable volume providing a dose of 8 mg, which allows for extended dosing intervals (up to 16 weeks).

The potency of aflibercept is evaluated though a bioassay that measures the ability of aflibercept to bind recombinant human VEGF121 (rhVEGF121) ligand and inhibit the effect of VEGF receptor activity in a transfected (b) (4) clonal cell line. The transfected (b) (4) cells express two chimeric receptors incorporating the VEGFR1 extracellular domain fused to the cytoplasmic domain of either IL18Rα or IL18Rβ, and an integrated NFκB luciferase-IRES-eGFP reporter gene.

Upon rhVEGF121 binding, the extracellular VEGFR1 dimerizes and the IL18Rα or IL18Rβ intracellular domains interact and can signal through the NFκB driven luciferase reporter gene. Potency results are reported as percentage relative to a qualified reference material. The drug substance (DS) manufacturing process consists of (b) (4)

The overall manufacturing control strategy incorporates (b) (4) The manufacturing processes and overall control strategies for Eylea HD (aflibercept) as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. The BLA is recommended for approval from a product quality perspective.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for the Drug Substance (DS) manufacturing facility, Regeneron Pharmaceuticals, Inc., (IOPS Rensselaer; Rensselaer, NY; FEI: 1000514603; pre-license inspection waived due to recent inspection history), and Drug Product (DP) manufacturing site, (b) (4) .

**List of Deficiencies to be Communicated**- N/A

**List of Post-Marketing Commitments/Requirements**

- PMC 4496-1: Post-marketing commitment to perform (b) (4)

- PMC 4496-2: Post-marketing commitment for real-world shipping studies, covering worst case shipping conditions (i.e., routes and modes of transportation, distance, duration, temperature, packing configuration, and shipping containers employed) on the final DP in the proposed container closure system to ensure there is no impact to product quality and sterility of the DP.

**Assessment of Common Technical Document- Quality Module 1**

Environmental Assessment of Claim of Categorical Exclusion

In Section 1.12.14, Regeneron requested categorical exclusion from the environmental assessment requirement under 21 CFR 25.15(d) and 21 CFR 25.31. These claims of categorical exclusions are acceptable for BLA 761355.

**Primary Container Labeling Assessment**
The OBP review of drug product labeling was performed by Liming Lu.

**Manufacturing Summary**
Facility Assessment Recommendation: Acceptable.

The proposed (b) (4) facility, Regeneron Pharmaceuticals, Inc. (FEI 1000514603), and the DS/DP testing facility, (b) (4)), are acceptable based on their currently acceptable cGMP compliance status and recent relevant inspectional coverage.

(b) (4)
are acceptable based on the previous acceptable inspectional history.

The proposed alternative (b) (4) manufacturer, (b) (4) was withdrawn from the current application on 6/5/2023.

**Office of Biotechnology Products Summary Recommendation**
Refer to the OPQ Executive Summary under the original BLA, uploaded to CDER Informatics Platform June 25, 2023, by Anshu Rastogi for background information. The pre-license inspections at the DP manufacturing site, (b) (4) identified a 3-item form FDA-483, Inspectional Observations and the firm did not provide adequate responses to address these observations during the original review cycle, leading to a withhold decision for the facility and a Complete Response was issued.

The information and data provided in the Resubmission and responses to information requests support that any residual issues/concerns have been addressed and the DP manufacturing facility is compliant. Overall, the manufacturing control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for Eylea HD (aflibercept) as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for at Regeneron Pharmaceuticals, Inc., (IOPS Rensselaer; Rensselaer, NY; FEI: 1000514603) and (b) (4) proposed for aflibercept DS and DP manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. The BLA is recommended for approval from a product quality, facility, microbiology and sterility assurance perspectives.

## 4.3. Nonclinical Pharmacology/Toxicology

The nonclinical development program was designed to evaluate the *in vivo* pharmacology and toxicology profiles of high dose aflibercept formulation. One new *in vivo* pharmacology study in rabbits and 2 new repeat-dose IVT toxicity studies in monkeys with monthly administration for 3 months (total of 4 injections) and 6 months (total of 7 injections) were conducted.

The pharmacology study conducted in a chronic retinal neovascularization (RNV) model in rabbits support the hypothesis that increasing the IVT dose of aflibercept in humans will result in a longer durability of effect. Eyes that received a single IVT dose of 2 mg/eye (corresponding to a human dose of approximately 8 mg/eye based on a vitreous volume of 1.17 mL in rabbits and 4.0 mL in humans) remained complete leak-free for a longer period compared to eyes that received 500 µg/eye (corresponding to a human dose of approximately 2 mg/eye).

The 3-month IVT toxicity study evaluated the marketing formulation at a concentration of 140 mg/mL (enriched with high molecular weight species). The 6-month IVT toxicity study evaluated several aflibercept formulations at concentrations of 80 or 140 mg/mL, with Formulation 2 having a similar composition as the marketing formulation except for a higher concentration of histamine ( (b) (4) mM in the marketing formulation). The formulation concentrations were 2 to 3.5X higher than the approved 40 mg/mL for EYLEA®.

The nonclinical safety profile of the high dose aflibercept formulations were generally comparable to the previously established safety profile of EYLEA®. Across studies with the aflibercept high dose formulations, there were no adverse ocular effects at any dose level. Ocular findings were limited to generally mild, transient ocular inflammation (low scores of aqueous cell or flare [0.5 to 1+] and/or vitreous cell [0.5 to 1+]) consistent with findings previously reported with the EYLEA formulation in the same species. The ocular NOAEL was the high dose 7 mg/eye. When normalized for vitreal volume (2 mL in monkeys and 4 mL in humans), the ocular NOAEL is 1.8-fold higher than the intended human dose of 8 mg.

In the 6-month ocular toxicity study, the only extraocular findings observed were microscopic changes in the respiratory epithelium of the nasal turbinates. The findings included erosion and/or ulceration (minimal to marked), squamous metaplasia (minimal to moderate), and hemorrhage (minimal to slight). The findings were observed at both doses evaluated, 4 and 7 mg/eye. There was no NOAEL. Most findings were reversible or showed partial reversibility during the 12-week recovery period.

The nasal turbinate findings were noted at doses ≥ 2 mg/eye of EYLEA®, with a NOAEL of 0.5 mg/eye. These findings are acknowledged in the EYLEA® label. The Applicant is using the same language as that accepted for EYLEA® with corrected exposure margin. At the NOAEL of 0.5 mg/eye in monkeys, the systemic exposure (AUC) for free aflibercept was approximately 3 times higher than the population pharmacokinetic estimated exposure observed in humans after an IVT dose of 8 mg. In the PULSAR, CANDELA, and PHOTON studies, an analysis of treatment emergent adverse events of nasomucosal findings was conducted with no indication of a safety signal in the 8 mg aflibercept groups compared to 2 mg. Dr. Rivera's Review recommended approval from a Pharmacology/Toxicology perspective.

## 4.4. Devices

| Packaging Component | Vial | Stopper |
|---|---|---|
| Description | (b) (4) glass, (b) (4) colorless, sterile | 13 mm, (b) (4) gray, (b) (4) (b) (4) sterile |
| Supplier Name | (b) (4) | (b) (4) |
| DMF Reference Number | DMF (b) (4) | DMF (b) (4)<br>DMF<br>DMF |

DMF, drug master file

### Vial and Stopper Release Testing Requirements

| Aspect | Method |
|---|---|
| Incoming QC Inspection[a] | In-house procedure |
| Dimensional Inspection[a] | |
| Visual Inspection[a] | |
| Quality | Vial: USP <660>, Ph. Eur. *3.2.1,* and JP <*7.01*><br>Stopper: USP <381>, Ph. Eur. 3.2.9, JP <7.03> |
| Sterility | USP <71> |
| Endotoxin | USP <85> |

[a] Test is performed as part of reduced testing.

EU, endotoxin unit; JP, Japanese Pharmacopeia; Ph. Eur, European Pharmacopeia; QC, Quality Control; USP, United States Pharmacopeia

This BLA submission includes only a single dose vial presentation containing 8 mg/0.07 ml of 114.3 mg/mL. The Eylea HD drug product is supplied as a vial with an injection kit
The injection kit contains :

- 30G ½ inch injection needle for intravitreal injection
- 18G 1½ inch 5 µm filter needle for withdrawal of the vial contents
- 1 ml syringe (made of (b) (4)) for administration.

Note: The injection kit, for both Eylea HD and Eylea, is a dispenser intended for ophthalmic use and is packaged with the drug with which it is intended to be used and, as such, was regulated as a drug and not as a combination product, in accordance with 21 CFR 200.50(c). This presentation matches that used in the single clinical trial, MYL- 1701P-3001, where similar safety and efficacy of Eylea HD vs Eylea® were demonstrated. Following the Genus Court decision this product is regulated as a combination product.

An Intercenter Consult Memorandum was obtained from the Office of Health Technology 3, Center for Devices and Radiologic Health (CDRH). The Summary is included below.

| | |
|---|---|
| **Device Presentation(s)** | Co-packaged syringe |
| Objective of this Memo: | Provide recommendation on the use of the co-packaged device constituent with the drug product, intended for intravitreal injection under review. |
| Review **Comments**: | The proposed device constituent is a 1 mL graduated syringe manufactured by (b) (4) (b) (4) under 510(k) (b) (4). This syringe is commonly selected by drug product manufacturers as the co-packed delivery device to be used with drug products intended for various ocular injections. In prior consulting reviews for the device constituent, we have cited gaps in the evaluation of biocompatibility given the 510(k) clearance of the syringe predates several revisions to the ISO 10993 series and corresponding Biocompatibility FDA Guidance. Consistent with our prior reviews, we recommend that the sponsor work with the syringe manufacturer, (b) (4) to evaluate the additional biocompatibility endpoint for ocular irritation. More specifically, we recommend that the sponsor evaluate intravitreal injection irritation, with a method similar to that used for ocular irritation testing per ISO 10993-23, with an additional criterion for the evaluation of white blood cell counts in the vitreous fluid from each eye. In prior reviews with this recommendation, subsequent internal discussion within the CDER review division resulted in a determination of minimal risk associated with ocular irritation and therefore no additional biocompatibility evaluation was requested of the sponsor. Therefore, we are deferring the lead CDER division for an evaluation of the biocompatibility benefit/risk profile to determine whether additional biocompatibility evaluation is needed and thus we are unable to make an approvability/disapprovability recommendation. |
| **Recommendation**: | Approvability Recommendation is deferred to CDER. |

### 4.6 Pediatric Waiver Request

The applicant has requested a waiver of pediatric assessments for AMD because pediatric studies are impossible or highly impracticable as AMD does not occur in the pediatric population. *The Division of Ophthalmology concurred with this waiver request.*

# 5. Sources of Clinical Data

## Listing of Clinical Studies for the Aflibercept Clinical Development Program

| Study Number Report Location | Study Population | Study Design Treatment Duration | Study Objectives | Treatment, Dose, and Regimen |
|---|---|---|---|---|
| VGFTe (HD)-AMD-1905 (CANDELA) Study 21086<br><br>Module 5.3.5.1<br><br>Completed (completion date: 30 Nov 2021) through Week 44 | Men or women ≥50 years of age with active subfoveal CNV secondary to nAMD | Phase 2, multicenter, randomized, single-masked, active-controlled<br><br>Treatment duration 44 weeks | **Primary:**<br>To determine the safety of HD aflibercept<br><br>To determine if HD aflibercept provides greater intraocular pharmacodynamic effect and/or longer duration of action compared to aflibercept 2 mg | Aflibercept IVT: 2 mg IAI: aflibercept 2 mg administered monthly as 3 initial injections (baseline, Weeks 4 and 8), followed by additional doses at Weeks 20 and 32[a] HD: aflibercept 8 mg administered monthly for 3 initial injections (baseline, Weeks 4 and 8), followed by additional doses at Weeks 20 and 32 |
| Study 20968 (PULSAR)<br>Module 5.3.5.1<br><br>Last participant last visit for the Week 48 primary endpoint: 27 Jul 2022 DBL: 24 Aug 2022<br><br>Ongoing (Week 48 completed) | Men or women ≥50 years of age with active subfoveal CNV secondary to nAMD | Phase 3, multicenter, randomized (1:1:1), double-masked, active-controlled<br><br>Treatment duration 96 weeks[b] | **Primary:**<br>To determine if treatment with HD aflibercept at intervals of 12 or 16 weeks provides non-inferior BCVA change compared to aflibercept 2 mg every 8 weeks in participants with nAMD<br><br>**Secondary:**<br>To determine the effect of HD versus aflibercept 2 mg on other visual and anatomic measures of response<br><br>To assess the efficacy of 8 mg compared to aflibercept 2 mg on vision-related quality of life<br><br>To evaluate the safety of aflibercept<br><br>To evaluate the PK and immunogenicity of aflibercept | Aflibercept IVT: 2q8: aflibercept 2 mg administered every 8 weeks after 3 initial monthly injections<br><br>HDq12: aflibercept 8 mg administered every 12 weeks after 3 initial monthly injections<br><br>HDq16: aflibercept 8 mg administered every 16 weeks after 3 initial monthly injections |
| VGFTe-HD-DME-1934 (PHOTON) Study 21091<br>Module 5.3.5.1<br>Last participant last visit for the Week 48 primary endpoint: 30 May 2022<br>DBL: 19 Aug 2022 | Men or women ≥18 years of age with type 1 or type 2 diabetes mellitus | Phase 2/3, multicenter, randomized (1:2:1), double-masked, active-controlled<br><br>Treatment duration 96 weeks[b] | **Primary:**<br>To determine if treatment with HD aflibercept at intervals of 12 or 16 weeks provides on-inferior BCVA change compared to aflibercept 2 mg dosed every 8 weeks<br><br>**Secondary:**<br>To determine the effect of HD versus aflibercept 2 mg on anatomic and other visual measures of response | Aflibercept IVT:<br>2q8: aflibercept 2 mg administered every 8 weeks after 5 initial monthly injections<br><br>HDq12: aflibercept 8 mg administered every 12 weeks after 3 initial monthly injections |

| | | | | |
|---|---|---|---|---|
| Ongoing (Week 48 completed) | | | To evaluate the safety, immunogenicity, and PK of aflibercept | HDq16: aflibercept 8 mg administered every 16 weeks after 3 initial monthly injections |

2q8=aflibercept 2 mg administered every 8 weeks; BCVA=best corrected visual acuity; DCO=data cut-off; HDq12=aflibercept 8 mg administered every 12 weeks; HDq16=aflibercept 8 mg administered every 16 weeks; IAI=intravitreal aflibercept injection; CNV=choroidal neovascularization; CSR=clinical study report; DME=diabetic macular edema; HD=high dose; IVT=intravitreal; nAMD=neovascular age-related macular degeneration; PK=pharmacokinetics; SAF=safety analysis set.

[a] Additional treatment could be given at Weeks 24, 28, 36, and 40 if participants met pre-specified criteria as defined in Module 5.3.5.1, CANDELA CSR.

[b] Studies are planned to be extended beyond Week 96 by approximately 1 year (60 weeks).

## 6. Review of Relevant Individual Trials Used to Support Efficacy

### Study 1: 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

**Trial Design**: Phase 2, multi-center, randomized, single-masked, 44-week study in participants with nAMD, 8 mg versus 2 mg. Participants were seen monthly through week 44. A total of approximately 100 eligible participants were randomized into 2 groups in a 1:1 ratio. Within each treatment group, 15 participants (total of 30) were also included in the dense PK substudy. The investigational product was administered intravitreally (IVT) monthly for 3 initial injections (baseline, week 4, and week 8), followed by additional doses at weeks 20 and 32. At week 16, additional treatment ("rescue") could be given after consultation with the Sponsor, if in the investigator's judgement, a patient could not adhere to the protocol-specified dosing interval due to persistent or worsening disease and required an interim injection. At weeks 24, 28, 36, and 40, participants were evaluated and given a dose (at their randomized dose level) if EITHER of the following criteria were met (pro re nata [PRN] criteria):

- Loss of ≥ 5 letters from week 20 Best Corrected Visual Acuity (BCVA) due to disease progression OR
- Anatomical findings that were considered vision-threatening, such as worsening or persistent retinal fluid, new or worsening retinal pigment epithelial detachment (PED), new or persistent hemorrhage, etc.

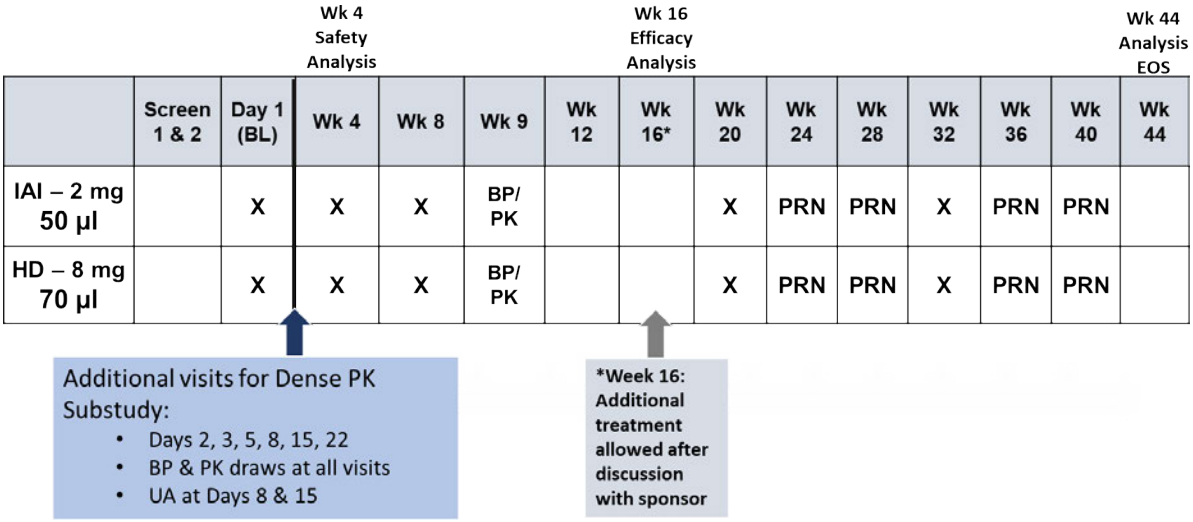
**Key Inclusion Criteria**

1. ≥50 years of age with active subfoveal CNV secondary to nAMD, including juxtafoveal lesions that affect the fovea in the study eye as assessed by an independent reading center
2. Best Corrected Visual Acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 78 to 24 (Snellen equivalent of 20/32 to 20/320) in the study eye

**Key Exclusion Criteria**

- Evidence of CNV due to any cause other than nAMD in either eye
- Subretinal hemorrhage in the study eye that is ≥50% of the total lesion area
- Prior use of IVT or systemic anti-VEGF agents (aflibercept, ranibizumab, bevacizumab, brolucizumab, pegaptanib sodium) or intraocular/periocular corticosteroids in the study eye

- Prior IVT investigational agents in either eye (e.g., anti-ang-2/anti-VEGF bispecific monoclonal antibodies, gene therapy)
- History of vitreoretinal surgery (including scleral buckling) in the study eye
- Pregnant or breastfeeding women, women of childbearing potential who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 90 days after the last dose.




Abbreviations: BL=baseline; BP=blood pressure; EOS=end of study; HD=high-dose aflibercept (8 mg) injection; IAI=intravitreal aflibercept (2 mg) injection; PK=pharmacokinetics; PRN=pro re nata; wk=week.

**Study Endpoints**

The primary efficacy endpoint was the proportion of participants without retinal fluid in the center subfield at week 16. The statistical analysis was performed using the chi-square test at the 2-sided 5% significance level. The 95% CIs were provided based on normal approximation.
For the primary analysis, missing post-baseline values for a given participant were imputed using the last observation carried forward (LOCF) procedure to determine the participant's primary efficacy response. Data from participants who received additional treatment were censored from the time additional treatment was administered at week 16. Participants were considered as non-responders if all post-baseline observations were missing.

**Reviewer's Comments:** *The primary efficacy endpoint is not considered by the Agency to be predictive of clinical benefit and would not be accepted to support the efficacy of the product. For the purposes of the Agency's review, best corrected visual acuity was assessed to evaluate efficacy.*

**Exploratory Efficacy Analysis**
For the categorical exploratory endpoints, analyses were performed in the same manner as for the primary efficacy analysis. The continuous exploratory endpoints (such as mean change in CRT, mean change in BCVA, mean change in lesion size and CNV size) were summarized descriptively. They were also analyzed using an analysis of covariance model with treatment as the main effect and baseline measurement as covariate.

**Compliance with Good Clinical Practices:** Studies were conducted in compliance with good clinical practice guidelines.

### Patient Disposition by Treatment Group (All Randomized Patients)

| | 2 mg (N=53) | 8 mg (N=53) |
|---|---|---|
| Number of patients who completed | 49 (92.5%) | 51 (96.2%) |
| Number of Patients who Discontinued from the Study | 4 (7.5%) | 2 (3.8%) |
| Adverse Event (Glioblastoma) | 0 | 1 (1.9%)[a] |
| Withdrawal of consent by subject | 4 (7.5%) | 1 (1.9%) |
| Study discontinuation due to COVID-19 | 1 (1.9%) | 0 |

Abbreviations: COVID-19=Coronavirus Disease 2019

[a] This event was not treatment-emergent, as it occurred after the end of the treatment-emergent study period (i.e., more than 30 days after last treatment).

### Table of Demographic Characteristics

| | 2 mg (N=53) | 8mg (N=53) |
|---|---|---|
| Gender | | |
| Male | 17 (32%) | 23 (43%) |
| Female | 36 (68%) | 30 (57%) |
| Ethnicity | | |
| Hispanic or Latino | 4 (7.5%) | 2 (3.8%) |
| Not Hispanic or Latino | 49 (92.5%) | 51 (96.2%) |
| Race | | |
| White | 51 (96%) | 52 (98%) |
| American Indian or Alaska native | 1 (2%) | 0 |
| Native Hawaiian or Other Pacific islander | 0 | 1 (2%) |
| Other | 1 (2%) | 0 |
| Age (years) | | |
| Mean (SD) | 77.7 (8.3) | 77.0 (7.7) |
| Median | 78.0 | 78.0 |
| Q1 : Q3 | 73: 83 | 70: 84 |
| Min : Max | 52 : 97 | 62 : 91 |
| ≥ 50-< 65 | 4 (7.5%) | 3 (5.7%) |
| ≥ 65 | 49 (92.5%) | 50 (94.3%) |
| Baseline BCVA (letters) in study eye | | |
| Mean (SD) | 58.2 (10.5) | 57.9 (13.6) |
| Median | 59.0 | 59.0 |
| Q1 : Q3 | 52.0: 66.0 | 53.0: 69.0 |
| Min : Max | 33: 75 | 23: 78 |
| Study eye mean baseline CRT (microns) (SD) | 488.1 (204.8) | 516.2 (175.6) |
| Median | 441.0 | 459.0 |
| Q1 : Q3 | 360.0: 527.0 | 409.0: 584.0 |
| Min : Max | 192: 1271 | 223: 1128 |
| Study eye mean baseline CNV area ($mm^2$) (SD) | 7.9 (6.2) | 7.5 (6.9) |
| Median | 6.3 | 5.3 |
| Q1 : Q3 | 4.6: 9.3 | 2.9: 9.7 |
| Min : Max | 1 : 39 | 0 : 34 |

**Efficacy**

## Proportion of Participants Without Fluid in the Center Subfield of the Study Eye, LOCF at Week 16 and Week 44 (Full Analysis Set)

| Treatment | Participants without Fluid | Difference (%) (95% CI) | p-value |
|---|---|---|---|
| Week 16 | | | |
| 8mg | 27/53 (51%) | 17% (-1.6, 35.5) | 0.077 |
| 2mg | 18/53 (34%) | | |
| Week 44 | | | |
| 8mg | 21/53 (40%) | 11% (-6.6, 29.2) | 0.2185 |
| 2mg | 15/53 (28%) | | |

Abbreviations: CI=confidence interval; IRF=intraretinal fluid; LOCF=last observation carried forward; SRF=subretinal fluid. No fluid=absence of IRF and/SRF in the center subfield. Center subfield=the circular area in 1 mm diameter centered around the center point of the fovea.

## Proportion Analysis of Patients Able to Maintain a 12 - Week Dosing Interval from Week 8 through Week 44 (Full Analysis Set)

| | 2 mg (N=53) | 8 mg (N=53) |
|---|---|---|
| All Full Analysis Patients | 53 | 53 |
| Patients that received at least one dose, n (%) | 53 (100%) | 53 (100%) |
| Patients dosed per-protocol*, n (%) | 24 (45.3%) | 29 (54.7%) |
| Patients not dosed at week 16, n (%) | 40 (75.5%) | 43 (81.1%) |
| Patients not dosed at any of week 16, 24 and 28, n (%) | 30 (56.6%) | 34 (64.2%) |
| Patients not dosed at any of week 16, 24, 28 and 36, n (%) | 28 (52.8%) | 33 (62.3%) |
| Patients not dosed at any of week 16, 24, 28, 36 and 40, n (%) | 26 (49.1%) | 30 (56.6%) |
| Patients with opportunity to reach week 16 [1], n (%) | 51/53 (96.2%) | 53/53 (100%) |
| Patients that had week 16 visit, n (%) | 48/53 (90.6%) | 53/53 (100%) |
| Patients not dosed at week 16, n (%) | 35/48 (72.9%) | 43/53 (81.1%) |
| Patients dosed at week 16, n (%) | 13/48 (27.1%) | 10/53 (18.9%) |
| Patients that had week 20 visit, n (%) | 51/53 (96.2%) | 53/53 (100%) |
| Patients not dosed at week 16, n (%) | 28/51 (54.9%) | 34/53 (64.2%) |
| Patients that had week 32 visit, n (%) | 50/53 (94.3%) | 51/53 (96.2%) |
| Patients not dosed at any of week 16 24 and 28**, n (%) | 28/50 (56.0%) | 33/51 (64.7%) |
| Patients that had week 36 visit, n (%) | 49/53 (92.5%) | 50/53 (94.3%) |
| Patients not dosed at any of week 16 24 and 28**, n (%) | 28/49 (57.1%) | 33/50 (66.0%) |
| Patients that had week 40 visit, n (%) | 49/53 (92.5%) | 51/53 (96.2%) |
| Patients not dosed at any of week 16, 24, 28 and 36**, n (%) | 25/49 (51.0%) | 32/51 (62.7%) |
| Patients that had week 44 visit, n (%) | 49/53 (92.5%) | 51/53 (96.2%) |
| Patients not dosed at any of week 16, 24, 28, 36 and 40**, n (%) | 24/49 (49.0%) | 29/51 (56.9%) |

**Mean Change from Baseline in BCVA Score (ETDRS Letters) in Study Eye – Line Plot by Visit, LOCF (Full Analysis Set)**

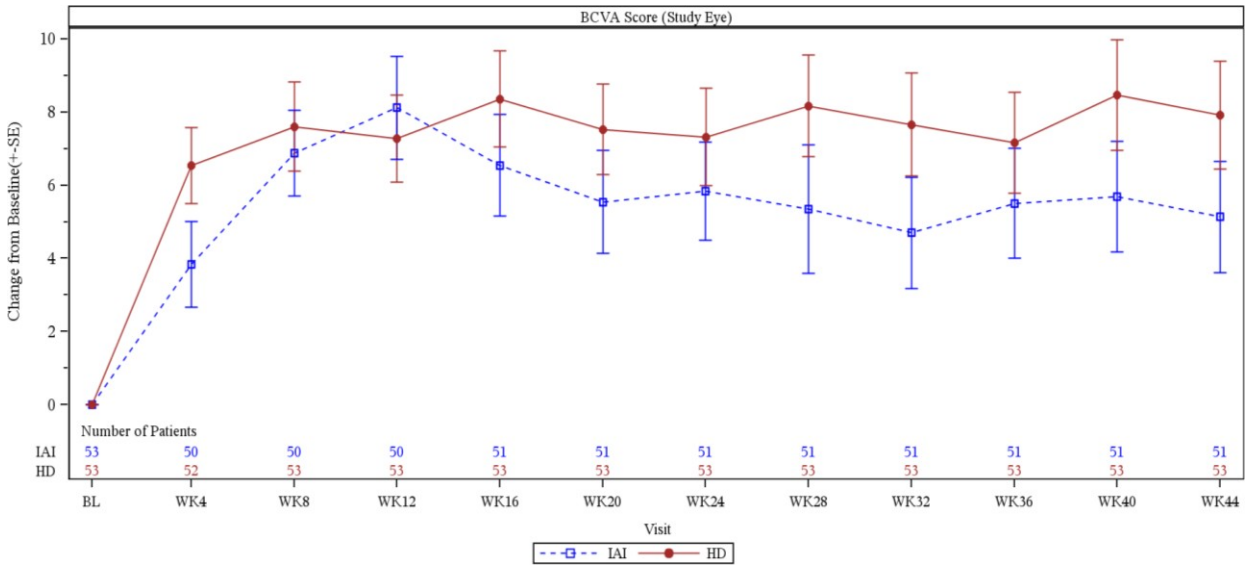
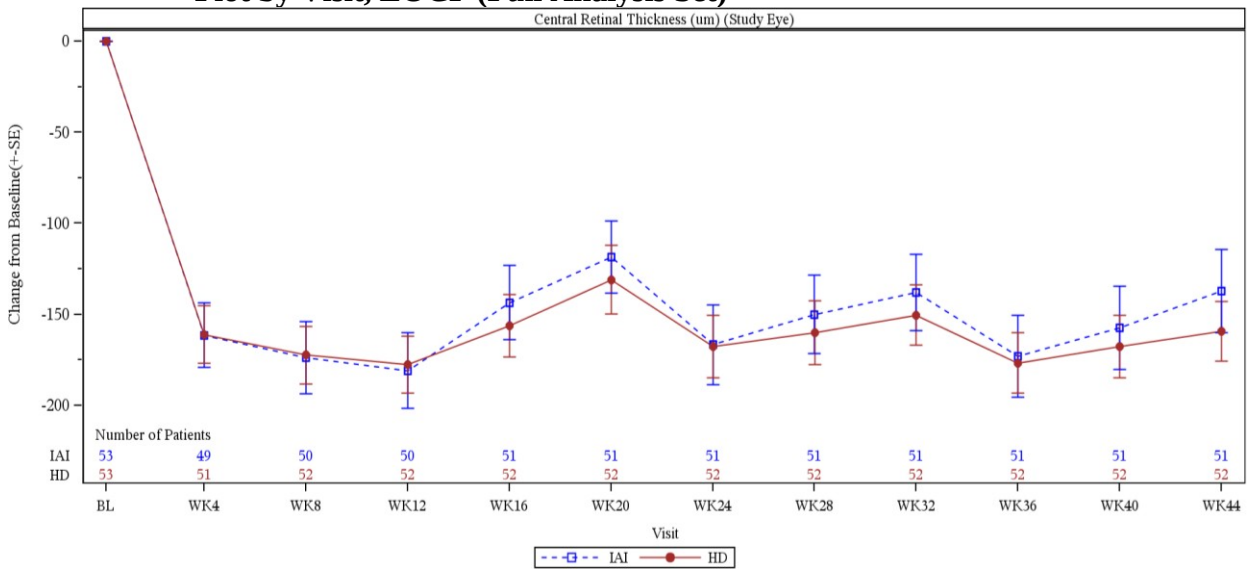



**Table 14.02.06/1.a ANCOVA of Change from Baseline in BCVA Score (ETDRS Letters) in Study Eye by Visit, LOCF (Full Analysis Set)**

| Visit | Treatment Group | Num. of Patients | Baseline (SD) | Means (SD) | Mean Change (SD) | p-value | Difference and 95% CI (LS mean) |
|---|---|---|---|---|---|---|---|
| Week 4 | 8 mg | 52 | 57.9 (13.7) | 64.5 (13.6) | 6.5 (7.5) | | 2.7 ( -0.4, 5.7) |
| Week 4 | 2 mg | 50 | 58.0 (10.7) | 61.9 (12.7) | 3.8 (8.3) | | |
| Week 8 | 8 mg | 53 | 57.9 (13.6) | 65.5 (13.9) | 7.6 (8.9) | | 0.7 ( -2.6, 4.0) |
| Week 8 | 2 mg | 50 | 58.0 (10.7) | 64.9 (12.6) | 6.9 (8.3) | | |
| Week 12 | 8 mg | 53 | 57.9 (13.6) | 65.2 (15.1) | 7.3 (8.7) | | -0.8 ( -4.5, 2.8) |
| Week 12 | 2 mg | 50 | 58.0 (10.7) | 66.2 (13.8) | 8.1 (9.9) | | |
| Week 16 | 8 mg | 53 | 57.9 (13.6) | 66.2 (15.0) | 8.4 (9.6) | 0.35 | 1.8 ( -2.0, 5.5) |
| Week 16 | 2 mg | 51 | 58.3 (10.7) | 64.8 (13.6) | 6.5 (9.9) | | |
| Week 20 | 8 mg | 53 | 57.9 (13.6) | 65.4 (15.2) | 7.5 (9.0) | | 1.9 ( -1.7, 5.7) |
| Week 20 | 2 mg | 51 | 58.3 (10.7) | 63.8 (14.5) | 5.5 (10.0) | | |
| Week 24 | 8 mg | 53 | 57.9 (13.6) | 65.2 (15.3) | 7.3 (9.7) | | 1.4 ( -2.3, 5.2) |
| Week 24 | 2 mg | 51 | 58.3 (10.7) | 64.1 (13.7) | 5.8 (9.6) | | |
| Week 28 | 8 mg | 53 | 57.9 (13.6) | 66.0 (16.1) | 8.2 (10.1) | | 2.8 ( -1.6, 7.2) |
| Week 28 | 2 mg | 51 | 58.3 (10.7) | 63.6 (16.3) | 5.4 (12.6) | | |
| Week 32 | 8 mg | 53 | 57.9 (13.6) | 65.5 (16.6) | 7.7 (10.2) | | 2.9 ( -1.2, 7.1) |
| Week 32 | 2 mg | 51 | 58.3 (10.7) | 63.0 (15.2) | 4.7 (10.9) | | |
| Week 36 | 8 mg | 53 | 57.9 (13.6) | 65.0 (15.7) | 7.2 (10.0) | | 1.6 ( -2.4, 5.7) |
| Week 36 | 2 mg | 51 | 58.3 (10.7) | 63.8 (14.6) | 5.5 (10.7) | | |
| Week 40 | 8 mg | 53 | 57.9 (13.6) | 66.3 (176.0) | 8.5 (11.0) | | 2.8 ( -1.5, 7.0) |
| Week 40 | 2 mg | 51 | 58.3 (10.7) | 63.9 (14.2) | 5.7 (10.8) | | |
| Week 44 | 8 mg | 53 | 57.9 (13.6) | 65.8 (16.2) | 7.9 (10.7) | 0.20 | 2.8 ( -1.4, 6.9) |
| Week 44 | 2 mg | 51 | 58.3 (10.7) | 63.4 (14.8) | 5.1 (10.8) | | |

/sasdata/Data/Production/BDM/VGFT/VGFT-HD-AMD/VGFTe-AMD-1905/Week44/Analysis_CSR/Programs/TFL/Generated/t_bcva_ancova_locf.sas (jin.li 29JUN2022 16:26 SAS Linux 9.4)

**Mean Change from Baseline in CRT (Central Subfield) in Study Eye – Line Plot by Visit, LOCF (Full Analysis Set)**




Abbreviations: CRT=central retinal thickness; HD=high-dose aflibercept (8 mg) injection; IAI=intravitreal aflibercept (2 mg) injection; LOCF=last observation carried forward; SE=standard error. LOCF=missing observations were imputed by the last non-missing post-baseline observation. For patients receiving additional treatment at week 16, measurements past week 16 were imputed using the last observation prior to additional treatment. Baseline: the latest available valid measurement taken on Study day 1prior to the administration of study drug. Source: Post-text Figure 14.02.08/5.b

**Summary of Ocular Treatment-Emergent Adverse Events of the Study Eye Reported in ≥ 2 Participants in Either Group Through Week 44 (Safety Analysis Set)**

| PT | 2 mg (n=53) | 8 mg (n=53) |
|---|---|---|
| **Number of Patients with at Least One Such AE, n (%)** | **20 (37.7%)** | **20 (37.7%)** |
| Vitreous detachment | 2 (3.8%) | 4 (7.5%) |
| Conjunctival hemorrhage | 2 (3.8%) | 3 (5.7%) |
| Dry eye | 2 (3.8%) | 2 (3.8%) |
| Neovascular age-related macular degeneration | 4 (7.5%) | 2 (3.8%) |
| Retinal tear | 0 | 2 (3.8%) |
| Punctate keratitis | 2 (3.8%) | 1 (1.9%) |
| Retinal hemorrhage | 2 (3.8%) | 1 (1.9%) |
| Visual acuity reduced | 2 (3.8%) | 1 (1.9%) |
| Visual impairment | 2 (3.8%) | 1 (1.9%) |

Abbreviations: AE=adverse event; HD=high-dose aflibercept (8 mg) injection; IAI=intravitreal aflibercept (2 mg) injection; MedDRA=medical dictionary for regulatory activities; PT=preferred term. MedDRA (Version 24.0) coding dictionary applied. TEAEs are defined as AEs occurring from the first dose of study drug to the last dose plus 30 days for participants who early discontinued, and for participants who completed the study (with week 44 visit), up to week 44 visit. The percentage is based on the number of participants in each treatment group as denominator. Source: Post-text Table 14.03.01/2-1.a

**Summary of Non-Ocular Treatment-Emergent Adverse Events in the Reported in ≥ 2 Participants in Either Group Through Week 44 (Safety Analysis Set)**

| PT | 2mg (n=53) | 8mg (n=53) |
|---|---|---|
| **Number of Patients with at Least One Such AE, n (%)** | **24 (45.3%)** | **28 (52.8%)** |
| Fall | 2 (3.8%) | 3 (5.7%) |
| Dizziness | 0 | 3 (5.7%) |
| COVID-19 | 2 (3.8%) | 2 (3.8%) |
| Diarrhea | 1 (1.9%) | 2 (3.8%) |
| Urinary tract infection | 1 (1.9%) | 2 (3.8%) |
| Nausea | 0 | 2 (3.8%) |
| Chest pain | 0 | 2 (3.8%) |
| Skin laceration | 0 | 2 (3.8%) |
| Sinusitis | 2 (3.8%) | 1 (1.9%) |
| Gastroesophageal reflux disease | 2 (3.8%) | 0 |
| Arthralgia | 2 (3.8%) | 0 |

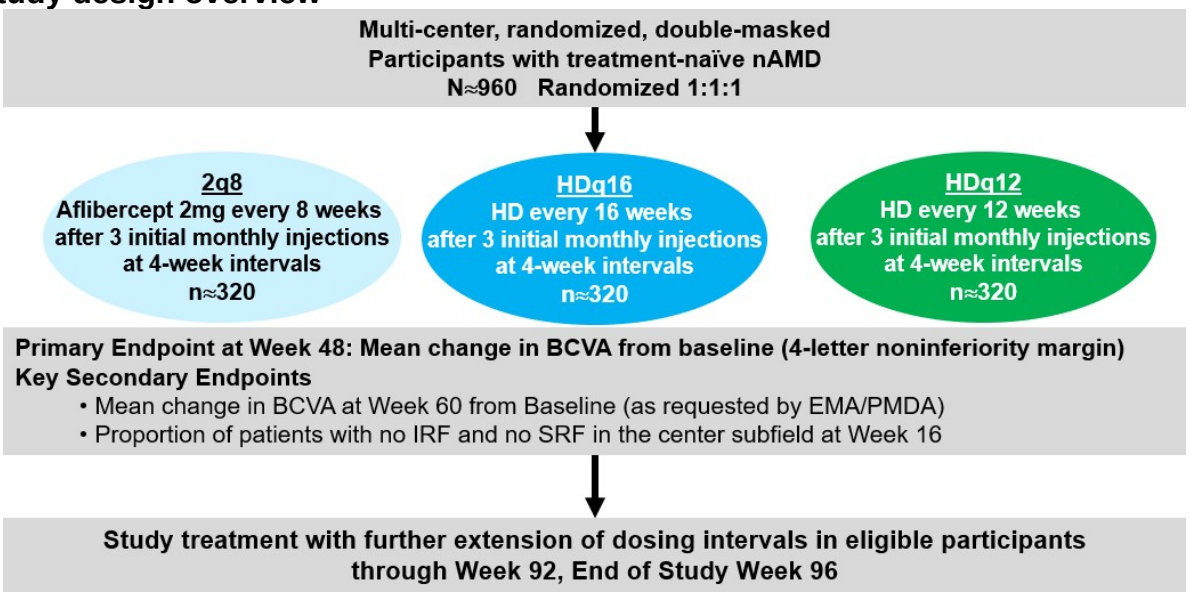
Abbreviations: AE=adverse event; HD=high-dose aflibercept (8 mg) injection; IAI=intravitreal aflibercept (2 mg) injection; MedDRA=medical dictionary for regulatory activities; PT=preferred term. MedDRA (Version 24.0) coding dictionary applied. TEAEs are defined as AEs occurring from the first dose of study drug to the last dose plus 30 days for participants who early discontinued, and for participants who completed the study (with week 44 visit), up to week 44 visit. The percentage is based on the number of participants in each treatment group as denominator. Source: Post-text Table 14.03.01/2-3.a

**Study 2:** 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

**Trial Design:** Phase 3, multi-center, randomized, double-masked, active-controlled study of IVT administration of 8 mg aflibercept versus 2 mg aflibercept in participants with **treatment-naïve nAMD**. The study continues to Week 96. Data up to Week 48 have been submitted. The study is ongoing.

## Study design overview




BCVA=best corrected visual acuity, EMA=European Medicines Agency, HD=8 mg 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.

## Dosing schedule

| | Day 1 | Wk 4 | Wk 8 | Wk 12 | Wk 16 | Wk 20 | Wk 24 | Wk 28 | Wk 32 | Wk 36 | Wk 40 | Wk 44 | Wk 48 (1° Endpoint) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2q8 | X | X | X | | X | o | X | o | X | o | X | o | X |
| HDq12 | X | X | X | | o[a] | X[a] | o | o | X[c] | o | o | X[c] | o |
| HDq16 | X | X | X | | o[b] | o[b] | X[b] | o | o | o | X[c] | o | o |

| | Wk 52 | Wk 56 | Wk 60 (Key 2° Endpoint) | Wk 64 | Wk 68 | Wk 72 | Wk 76 | Wk 80 | Wk 84 | Wk 88 | Wk 92 | Wk 96 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2q8 | o | X | o | X | o | X | o | X | o | X | o | |
| HDq12 | o | X[d] | o | o | X[d] | o | o | X[d] | o | o | X[d] | |
| HDq16 | o | X[d] | o | o | o | X[d] | o | o | o | X[d] | o | |

1º=primary, 2º=secondary, DRM=dose regimen modification, HD=high dose, IXRS=Interactive Response System, q8=every 8 weeks, q12=every 12 weeks, q16=every 16 weeks, Wk=Week, X=active injection, o=sham procedure

For masking purposes, DRM assessments were performed in all participants at all visits (through the IXRS) starting from Week 16.

a. HDq12 group: If DRM criteria were met at Week 16 or 20, participants continued on q8 rescue regimen.
b. HDq16 group: If DRM criteria were met at Week 16 or 20, participant continued on q8 rescue regimen. If DRM criteria were met at Week 24, participant continued on q12 regimen.
c. For participants remaining on a dosing interval of q12 or q16 weeks after Week 24, if DRM criteria are met at an active injection visit, the next dosing interval will be reduced by 4 weeks (to a minimum of q8).
d. From Week 52, all participants in HD groups will be eligible for dose interval shortening (to a minimum of q8) or extension (by 4-week increments) according to pre-specified DRM criteria. If DRM criteria are met at an active injection visit, the next dosing interval will be changed by 4 weeks.

This figure does not reflect all available dosing options, once a participant's dose regimen is shortened or extended.
This study started prior to the onset of the 2022 crisis between Russia and Ukraine and included study sites located in Ukraine and in Russia. All participants affected by the crisis, related findings and deviations by unique participant identifier and by investigational site, and a description of the finding or deviation were recorded.

Only one eye was treated within the study. Sham procedures were done on visits when an active injection is not planned. No sham or active procedures were done at the non-treatment visit at Week 12. At all subsequent visits, all participants are receiving either active study treatment injection or sham procedure, depending on their assigned treatment schedule and eligibility for dose regimen modification (DRM).

Starting at Week 16, participants assigned to HDq12 or HDq16 were assessed for DRM criteria at every visit:

- If a participant in the HDq12 group or the HDq16 group met DRM criteria at Week 16 or Week 20, the participant was dosed with 8 mg aflibercept at that visit and subsequently continued receiving 8 mg aflibercept every 8 weeks.
- A participant in the HDq16 group who had not met DRM criteria at Week 16 or Week 20 and met DRM criteria at Week 24 was dosed with 8 mg aflibercept at that visit and subsequently continued receiving 8 mg aflibercept every 12 weeks.
- Subsequently, participants who meet DRM criteria at any active treatment visit would have their intervals shortened by 4 weeks, to a minimum interval of 8 weeks. Starting at Week 52, all participants randomized to HDq12 or HDq16 were eligible for adjustments of their treatment intervals (shortening or extension) based on pre-specified DRM criteria, with the dose interval adjustments (shortening or extension) becoming effective at or after Week 60 (after data collection for key secondary efficacy endpoint). Participants could also be eligible for extensions of their treatment intervals according to additional DRM criteria, which are assessed in parallel with the previous shortening criteria.
- All participants were examined every 4 weeks through Week 96.

### Dose Regimen Modification (DRM)/Rescue Regimen

For masking purposes, assessments for DRM were performed in all participants at all visits (through the IXRS) starting from Week 16. Based on these assessments, participants in the HD groups could have their treatment intervals shortened or extended. The minimum interval between injections will be 8 weeks, which is considered a rescue regimen for participants randomized to HD aflibercept who are unable to tolerate a dosing interval greater than every 8 weeks. Participants in the aflibercept 2 mg group remained on fixed q8 dosing throughout the study until the end of masked study visit at Week 96 (i.e., no modifications of their treatment intervals regardless of the outcomes of the DRM assessments).

**Reviewer's Comments:** *The Agency disagreed with the unequal treatment of the participants in different treatment regimens.*

**DRM in Year 1: Baseline to Week 48**

Beginning at Week 16, participants in the 8 mg groups had the dosing interval shortened (at the visits described below) if BOTH the following DRM criteria are met:

- BCVA loss >5 letters from Week 12, AND
- >25 µm increase in central retinal thickness (CRT) from Week 12 OR new foveal hemorrhage OR new foveal neovascularization

In case the Week 12 measurement was not available, the Week 8 measurement was used instead. If both, Week 12 and Week 8 measurements were not available, the Week 4 measurement was used. If a participant in the HDq12 group or the HDq16 group met both criteria at Week 16 or Week 20, the participant was dosed with 8 mg aflibercept at that visit and would continue on rescue regimen (aflibercept 8 mg, every 8 weeks). If a participant in the HDq16 group who had not met the criteria at Week 16 or Week 20 met both criteria at Week 24, the participant was dosed with 8 mg aflibercept at that visit and would continue on q12 dosing.

For participants whose interval was not shortened to q8 dosing at or before Week 24, the interval was shortened if the DRM criteria were met at subsequent visits with active injection. Participants in the HDq12 group who met the criteria would receive the planned dose at that visit and would then continue on rescue regimen (aflibercept 8 mg, every 8 weeks).

Participants in the HDq16 group who meet these criteria would receive the planned dose at that visit and will then continue to be dosed every 12 weeks if they were on a 16-week interval, or switch to the rescue regimen (aflibercept 8 mg, every 8 weeks) if they were on a 12-week interval. Therefore, a participant randomized to HDq16 whose injection interval has been shortened to q12 would have their injection interval further shortened to q8 if these criteria were met at any subsequent assessment.

**DRM Year 2: Week 52 to Week 96 (End of Masked Part of Study)**

From Week 52 through the end of the masked part of study (Year 2), all participants in the HD groups would continue to have the interval shortened in 4-week intervals (to a minimum of q8) if the DRM criteria for shortening were met at visits with active injection, using the criteria described above for Year 1.

In addition to shortening of the interval, all participants in the HD groups (including HD group participants whose interval was shortened during Year 1) were eligible for interval extension (by 4-week increments) if the following DRM criteria were met at visits with active injection in Year 2:

- BCVA loss <5 letters from Week 12, AND
- No fluid at the central subfield on OCT, AND
- No new onset foveal hemorrhage or foveal neovascularization

For participants who did not meet the criteria for shortening or extension of the interval, the dosing interval was maintained. As in Year 1, all participants in all treatment groups (including the 2q8 group) were evaluated against both DRM criteria at all visits through the IXRS for masking purposes. However, changes to dosing schedule were only implemented as described above. No changes to the dosing schedule were made to the 2q8 treatment group at any time. All anatomic criteria were based on the site evaluations/OCT assessments, not on the reading center assessments.

**DRM Year 3 (Masked Transition Period and Open-label Extension Part): Week 96 to Week 156 (End of Study) / E-DRM Criteria**

The E-DRM criteria refer to new baseline (NB) which was defined as the average of values assessed at Weeks 84, 88, and 92 (with the average being rounded up to the next integer). At Week 96, no interval adjustments will be performed for any group.

Beginning at Week 100, all participants will have the dosing interval **shortened** if the following criteria are met at ANY visit (scheduled or unscheduled, with or without active injection):

1. BCVA loss >5 letters from NB BCVA due to persistent or worsening AMD, AND
2. Any of the following
   - >25 µm increase in CRT from NB CRT
   - new onset of foveal neovascularization
   - new foveal hemorrhage

   OR
3. BCVA loss >10 letters NB due to worsening AMD

If the E-DRM shortening criteria are met at any treatment, monitoring or unscheduled visit, the participant will be dosed at the same visit. If the E-DRM criteria are met at a dosing visit the subsequent interval will be shortened by 2 weeks. If the E-DRM criteria are met at a non-dosing visit, the subsequent interval will be shortened to the time from the most recent dose minus 2 weeks. Participants can be seen for unscheduled visits at any time at the investigator's discretion. Treatment intervals may not be adjusted to less than 8 weeks. Actual intervals may be slightly shorter due to the windows allowed for visits planned 8 weeks apart.

If a participant does not meet any of the E-DRM criteria but is deemed at high risk for vision loss, the participant should be brought back for evaluation within approximately 2 weeks. If E-DRM criteria are still not met, and the investigator feels there is high risk for irreversible disease progression, a dose can be given at that visit, and the subsequent interval will be shortened to the time from the most recent dose minus 2 weeks. The minimum dosing interval remains every 8 weeks (q8).

Similar to Year 2, all participants in all groups (including participants whose interval was shortened during Year 1, Year 2, or Year 3) are eligible for interval **extension** up to a maximum interval of 24 weeks, but in contrast to Year 2, intervals will now be modified by 2-week rather than 4-week increments, if all of the following E-DRM criteria are met at visits with active injection:

1. BCVA loss <5 letters from the NB, AND
2. No fluid at the central subfield on OCT, AND
3. No new onset foveal hemorrhage or foveal neovascularization

For participants who do not meet the criteria for shortening or extension of the interval, the dosing interval will be maintained. For E-DRM adjustment purposes, similar to the masked study part, all anatomic criteria will be based on the local site evaluations/OCT assessments, not on the assessments of the central reading center.

**Key Inclusion Criteria**

1. ≥18 years of age with type 1 or type 2 diabetes mellitus
2. DME with central involvement in the study eye with CRT ≥300 μm (or ≥320 μm on Spectralis) as determined by the reading center at the screening visit
3. Best Corrected Visual Acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 78 to 24 (Snellen equivalent of 20/32 to 20/320) in the study eye with decreased vision determined to be primarily the result of DME

**Key Exclusion Criteria**

1. Evidence of macular edema due to any cause other than diabetes mellitus in either eye
2. Active proliferative diabetic retinopathy in the study eye
3. Panretinal laser photocoagulation (PRP) or macular laser photocoagulation in the study eye within 12 weeks (84 days) of the screening visit
4. IVT anti-VEGF treatment (aflibercept, ranibizumab, bevacizumab, brolucizumab, pegaptanib sodium) in the study eye within 12 weeks (84 days) of the screening visit
5. Prior IVT investigational agents in either eye (e.g., anti-ang-2/anti-VEGF bispecific monoclonal antibodies, gene therapy, etc.) at any time
6. Treatment with ocriplasmin (JETREA®) in the study eye at any time
7. Previous use of intraocular or periocular corticosteroids in the study eye within 16 weeks (112 days) of the screening visit, or ILUVIEN® or OZURDEX® IVT implants at any time
8. History of vitreoretinal surgery (including scleral buckle) in the study eye
9. Any other intraocular surgery within 12 weeks (84 days) before the screening visit
10. Yttrium-aluminum-garnet (YAG) laser capsulotomy in the study eye within 4 weeks (28 days) of the screening visit
11. IOP ≥25 mmHg in the study eye
12. History of glaucoma filtration surgery in the past, or likely to need filtration surgery in the future in the study eye
13. Evidence of infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye within 4 weeks (28 days) of the screening visit
14. Any intraocular inflammation/infection in either eye within 12 weeks (84 days) of the screening visit
15. History of idiopathic or autoimmune uveitis in the study eye
16. Vitreomacular traction or epiretinal membrane in the study eye evident on biomicroscopy or OCT that is thought to affect central vision
17. Preretinal fibrosis involving the macula in the study eye
18. Any history of macular hole of stage 2 and above in the study eye
19. Current iris neovascularization, vitreous hemorrhage, or tractional retinal detachment visible at the screening assessments in the study eye
20. History of corneal transplant or corneal dystrophy in study eye
21. Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the patient beyond what is to be expected from standard procedures of IVT injections, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety
22. Only 1 functional eye, even if that eye was otherwise eligible for the study (e.g., BCVA of counting fingers or less in the eye with worse vision)
23. Structural damage to the center of the macula in the study eye that is likely to preclude improvement in BCVA following the resolution of macular edema including atrophy of the

retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia, or organized hard exudates
24. Ocular conditions with poorer prognosis in the fellow eye
25. Inability to obtain photographs, FA, or SD-OCT in the study eye, e.g., due to media opacity, allergy to fluorescein dye, or lack of venous access
26. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the patient at high risk for treatment complications
27. Any prior systemic (IV) anti-VEGF administration
28. Uncontrolled diabetes mellitus as defined by hemoglobin A1c (HbA1c) > 12%
29. Uncontrolled blood pressure (defined as systolic >160 mmHg or diastolic >95 mmHg). Patients may be treated with up to 3 agents known to have anti-hypertensive effects for arterial hypertension to achieve adequate blood pressure control. This limit applies to drugs that could be used to treat hypertension even if their primary indication in the patient was not for blood pressure control. Any recent changes in medications known to affect blood must be stable for 12 weeks (84 days) prior to screening.
30. History of cerebrovascular accident or myocardial infarction within 24 weeks (168 days) of screening visit
31. Renal failure, dialysis, or history of renal transplant
32. Known sensitivity to any of the compounds of the study formulation
33. Participation in an investigational study within 30 days prior to screening visit that involved treatment with any drug (excluding vitamins and minerals) or device
34. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the sponsor
35. Pregnant or breastfeeding women
36. Men or women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 3 months after the last dose.

Participants were randomly assigned in a 1:1:1 ratio to 1 of 3 parallel treatment groups. Randomization was stratified by geographic region (Japan vs. Rest of World), and baseline (Day 1) BCVA (< 60 vs. ≥ 60), to ensure balanced distribution of the treatment groups within each stratum.

Only 1 eye per participant could be enrolled in the study. If a participant's fellow (non-study) eye required anti-VEGF treatment during the participant's participation in the study, the fellow eye should have been treated with aflibercept 2 mg according to the approved treatment regimen in the respective country/region, irrespective of the randomization assignment of the participant. Although the fellow eye could have received treatment, it was not considered an additional study eye. Participants who received treatment for the fellow eye remained in the study.

**Disposition in overall study: Week 48 (all enrolled participants)**

| Number of subjects | 2q8 | HDq12 | HDq16 |
|---|---|---|---|
| Randomized, n (%) | 337 (100%) | 336 (100%) | 338 (100%) |
| Treated, n (%) | 336 (99.7%) | 335 (99.7%) | 338 (100%) |
| Completed study until week 48, n (%) | 309 (91.7%) | 316 (94.0%) | 312 (92.3%) |
| Unknown if completed study until week 48 [a], n (%) | 3 (0.9%) | 2 (0.6%) | 1 (0.3%) |
| Did not complete study until week 48, n (%) | 25 (7.4%) | 18 (5.4%) | 25 (7.4%) |
| Primary reason | | | |
| Adverse event | 5 (1.5%) | 1 (0.3%) | 5 (1.5%) |
| Physician decision | 1 (0.3%) | 3 (0.9%) | 2 (0.6%) |
| Protocol deviation | 0 | 1 (0.3%) | 1 (0.3%) |
| Lost to follow-up | 1 (0.3%) | 1 (0.3%) | 0 |
| Lack of efficacy | 2 (0.6%) | 0 | 0 |
| Withdrawal by subject | 5 (1.5%) | 5 (1.5%) | 12 (3.6%) |
| Death | 5 (1.5%) | 3 (0.9%) | 1 (0.3%) |
| Other | 4 (1.2%) | 2 (0.6%) | 2 (0.6%) |
| COVID-19 pandemic | 2 (0.6%) | 2 (0.6%) | 2 (0.6%) |
| Subject decision: COVID-19 pandemic related | 2 (0.6%) | 2 (0.6%) | 2 (0.6%) |

[a]6 participants who had missing Week 48 information (i.e., they neither discontinued during Week 48 time frame, nor had Week 48 visit performed or marked as not done) were summarized as Unknown if completed study until Week 48 (see Database errata in Section 16.4.2).

**Demographics and disease characteristics (full analysis set)**

| | 2q8 | 8mg q12 | 8 mg q16 |
|---|---|---|---|
| | N = 336 | N = 335 | N = 338 |
| Gender, n (%) | | | |
| Female | 188 (56.0%) | 182 (54.3%) | 180 (53.3%) |
| Male | 148 (44.0%) | 153 (45.7%) | 158 (46.7%) |
| Race, n (%) | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 83 (24.7%) | 74 (22.1%) | 77 (22.8%) |
| Asian Indian | 0 | 0 | 0 |
| Chinese | 40 (11.9%) | 31 (9.3%) | 31 (9.2%) |
| Japanese | 34 (10.1%) | 31 (9.3%) | 33 (9.8%) |
| Korean | 9 (2.7%) | 11 (3.3%) | 12 (3.6%) |
| Thai | 0 | 0 | 0 |
| Other | 0 | 1 (0.3%) | 1 (0.3%) |
| Black or African American | 2 (0.6%) | 2 (0.6%) | 0 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| White | 249 (74.1%) | 256 (76.4%) | 260 (76.9%) |
| Not reported | 2 (0.6%) | 2 (0.6%) | 1 (0.3%) |
| Multiple | 0 | 1 (0.3%) | 0 |
| Hispanic or Latino | 12 (3.6%) | 7 (2.1%) | 9 (2.7%) |
| Not Hispanic or Latino | 322 (95.8%) | 322 (96.1%) | 326 (96.4%) |
| Not reported | 2 (0.6%) | 6 (1.8%) | 3 (0.9%) |
| Age (years) n | | | |
| Mean (SD) | 74.2 (8.8) | 74.7 (7.9) | 74.5 (8.5) |
| Median | 74.0 | 75.0 | 75.0 |
| Min, Max | 50,96 | 52,93 | 53,95 |
| Age group (years) , n (%) < 65 | 45 (13.4%) | 26 (7.8%) | 43 (12.7%) |
| ≥ 65 to < 75 | 126 (37.5%) | 137 (40.9%) | 124 (36.7%) |
| ≥ 75 to < 80 | 69 (20.5%) | 77 (23.0%) | 66 (19.5%) |
| ≥ 80 to < 85 | 59 (17.6%) | 59 (17.6%) | 66 (19.5%) |
| ≥ 85 | 37 (11.0%) | 36 (10.7%) | 39 (11.5%) |
| Mean BCVA (ETDRS letter score) (SD) | 58.9 (14.0) | 59.9 (13.4) | 60.0 (12.4) |

| | | | |
|---|---|---|---|
| Median BCVA (ETDRS letter score) | 62.0 | 62.0 | 61.0 |
| BCVA: Min, Max | 24,78 | 24,78 | 24,78 |
| Categorized BCVA (ETDRS letters score), n (%) | | | |
| ≤ 73 | 287 (85.4%) | 293 (87.5%) | 290 (85.8%) |
| > 73 | 49 (14.6%) | 42 (12.5%) | 48 (14.2%) |
| Categorized BCVA (ETDRS letters score), n (%) [a] | | | |
| < 60 | 136 (40.5%) | 141 (42.1%) | 144 (42.6%) |
| ≥ 60 | 200 (59.5%) | 194 (57.9%) | 194 (57.4%) |
| Intraocular Pressure (mmHg) Mean (SD) | 14.8 (3.0) | 14.9 (3.2) | 14.9 (3.2) |
| Intraocular Pressure (mmHg) Median | 15.0 | 15.0 | 15.0 |
| Intraocular Pressure Min, Max | 6,25 | 7,25 | 7,25 |
| Geographic atrophy (as per reading center), n (%) | | | |
| No | 328 (97.6%) | 326 (97.3%) | 326 (96.4%) |
| Yes | 3 (0.9%) | 3 (0.9%) | 6 (1.8%) |
| Not available | 5 (1.5%) | 6 (1.8%) | 6 (1.8%) |
| Polypoidal choroidal vascularization (as per reading center), n (%) | | | |
| No | 53 (15.8%) | 54 (16.1%) | 46 (13.6%) |
| Yes | 54 (16.1%) | 45 (13.4%) | 42 (12.4%) |
| Not available | 1 (0.3%) | 2 (0.6%) | 0 |
| Missing | 228 (67.9%) | 234 (69.9%) | 250 (74.0%) |
| Central subfield retinal thickness (µm, as per reading center) | | | |
| Mean (SD) | 367.1 (133.6) | 370.3 (123.7) | 370.7 (132.7) |
| Median | 343.0 | 348.0 | 340.0 |
| Min, Max | 142,1116 | 151,840 | 144,913 |
| Choroidal neovascularization size ($mm^2$, as per reading center) | | | |
| Mean (SD) | 6.359 (5.039) | 5.977 (4.831) | 6.546 (5.532) |
| Median | 4.997 | 4.899 | 4.698 |
| Min, Max | 0.148,24.129 | 0.115,30.023 | 0.000, 28.650 |
| Total lesion area ($mm^2$, as per reading center) | | | |
| Mean (SD) | 6.86 (5.41) | 6.38 (5.07) | 6.88 (5.65) |
| Median | 5.41 | 5.03 | 5.07 |
| Min, Max | 0.148,27.41 | 0.185,30.02 | 0.180,28.65 |
| Choroidal neovascularization type (as per reading center), n (%) | | | |
| Type 1 - occult or PCV | 194 (57.7%) | 198 (59.1%) | 191 (56.5%) |
| Type 2 - classic CNV | 66 (19.6%) | 68 (20.3%) | 61 (18.0%) |
| Type 1 and Type 2 – both classic and occult are present | 66 (19.6%) | 59 (17.6%) | 74 (21.9%) |
| Type 3 – RAP | 5 (1.5%) | 4 (1.2%) | 5 (1.5%) |
| Cannot grade | 0 | 0 | 1 (0.3%) |
| Not applicable - no CNV present | 5 (1.5%) | 6 (1.8%) | 6 (1.8%) |

**Summary of Treatment Exposure in Study Eye through Week 48 (Pulsar Safety Analysis Set)**

| | **2q8** (N=336) | **HDq12** (N=325) | **HDq16** (N=338) |
|---|---|---|---|
| Total number of active injections | 2267 | 1986 | 1703 |
| Total number of sham injections | 1212 | 1515 | 1793 |
| 1 active injection per patient, n (%) | 1 (0.3%) | 2 (0.6%) | 2 (0.6%) |
| 2 active injections per patient, n (%) | 1 (0.3%) | 2 (0.6%) | 1 (0.3%) |
| 3 active injections per patient, n (%) | 4 (1.2%) | 3 (0.9%) | 9 (2.7%) |
| 4 active injections per patient, n (%) | 6 (1.8%) | 7 (2.1%) | 22 (6.5%) |
| 5 active injections per patient, n (%) | 6 (1.8%) | 22 (6.6%) | 263 (77.8%) |
| 6 active injections per patient, n (%) | 29 (8.6%) | 260 (77.6%) | 11 (3.3%) |
| 7 active injections per patient, n (%) | 288 (85.7%) | 39 (11.6%) | 29 (8.6%) |
| 8 active injections per patient, n (%) | 1 (0.3%) | 0 | 0 |
| Mean number of injections (SD) | 6.7 (0.8) | 5.9 (0.8) | 5.1 (0.8) |
| Median number of injections | 7.0 | 6.0 | 5.0 |
| Min: Max | 1: 8 | 1: 7 | 1: 7 |

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; 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; The percentage was based on the number of patients in each treatment group as a denominator. Study drugs given at week 48 or beyond were not included in this table. Patients in the HD groups could have had their interval shortened if protocol specified criteria were met.

**Efficacy**

## Change from baseline in BCVA measured by the ETDRS letter score at Week 48, MMRM (full analysis set)

| | **2mg q8** N = 336 | **8mg q12** N = 335 | **8mg q16** N = 338 |
|---|---|---|---|
| Baseline mean[a] | 58.9 | 59.9 | 60.0 |
| Number of subjects with Week 48 data | 285 | 299 | 289 |
| Arithmetic mean (SD) change from baseline[a] | 7.6 (12.2) | 6.7 (12.6) | 6.2 (11.7) |
| LS mean (SE) change from baseline | 7.0 (0.7) | 6.1 (0.8) | 5.9 (0.7) |
| Degrees of freedom | | 622.1 | 647.7 |
| Comparison[b] | | HDq12 - 2q8 | HDq16 - 2q8 |
| t-value | | 3.14 | 3.07 |
| p-value of one-sided test for non-inferiority at a margin of 4 letters | | 0.0009 | 0.0011 |
| Estimate for Contrast and two-sided 95% CI[c] | | -1.0 (-2.9,0.9) | -1.1 (-3.0,0.7) |

BCVA = best corrected visual acuity, CI = Confidence interval, LS = Least Square, SD = Standard deviation, SE = Standard error. A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [< 60 vs. ≥ 60]) as fixed factors, and terms for the interaction between baseline BCVA and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: unstructured. Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints as described in Table 9-12 in Section 9.5 of the SAP.

[a]Based on observed assessments.

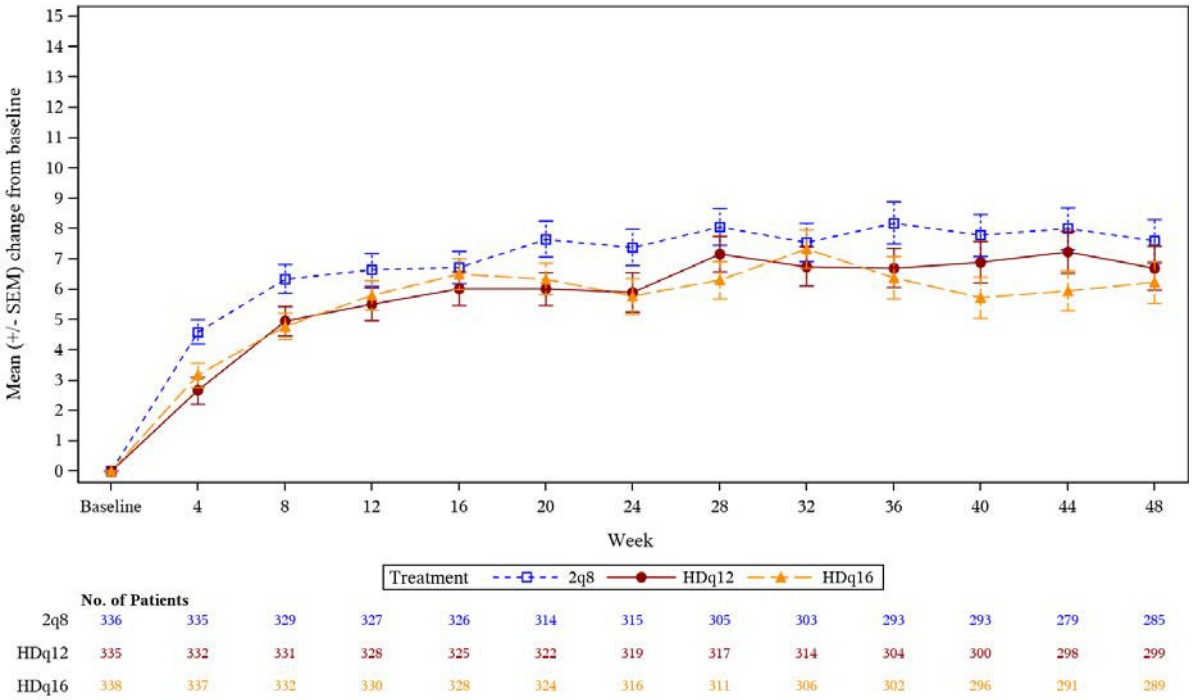
[b]The contrast also includes the interaction term for treatment x visit (at Week 48, for details on the population-level summary see SAP Section 6.2.2.1).

[c]Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively, with two-sided 95% CIs.

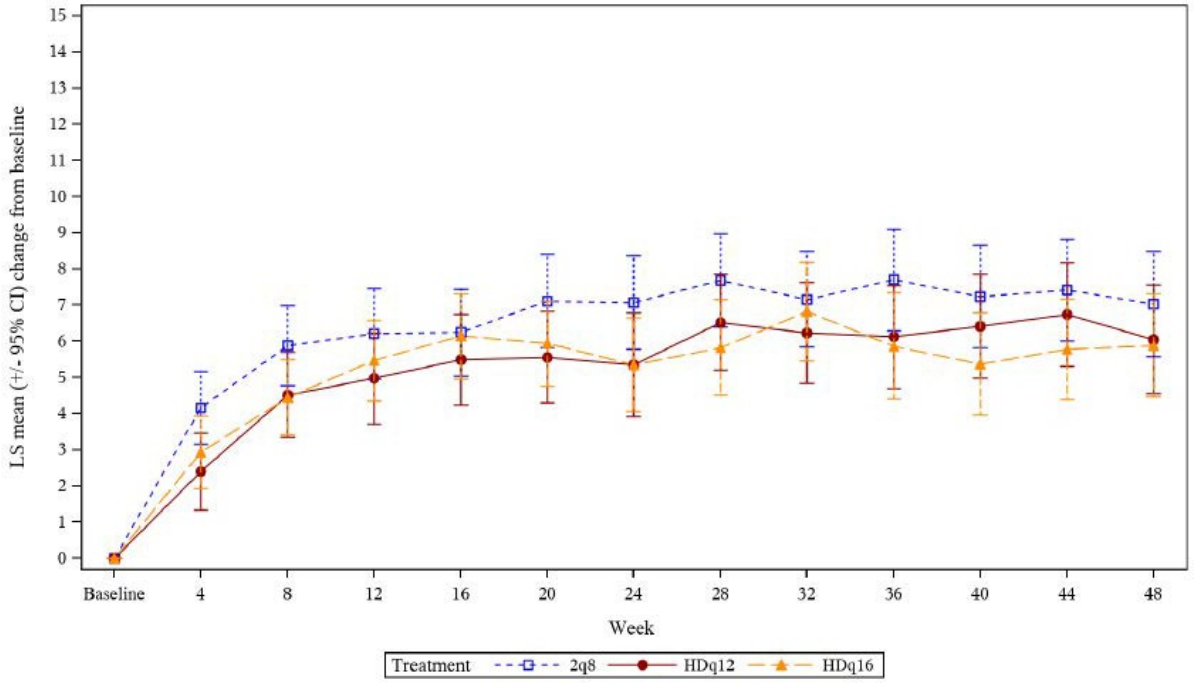
See Definition of terms for treatment group description. Source: Table 14.2.1/1

**Reviewer's Comments:** *Multiple sensitivity analyses were consistent with these findings.*

**Mean change from baseline in BCVA measured by the ETDRS letter score, Observed Cases (full analysis set)**




**LSmean change from baseline in BCVA measured by the ETDRS letter score, MMRM (full analysis set)**




BCVA = best corrected visual acuity, ETDRS = Early Treatment of Diabetic Retinopathy Study, SEM= standard error mean OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded as described in the SAP. LS = least squares, SEM= standard error of the LS mean. Source: Figures 14.2.1/1 and 14.2.1/1.1

## Secondary Endpoints:

**Proportion of participants with no IRF and no SRF in central subfield at Week 16, LOCF (full analysis set)**

| | 2mg q8<br>N = 336 | 8mg q12<br>N = 335 | 8mg q16<br>N = 338 |
|---|---|---|---|
| Subjects who had no IRF and no SRF | 173/335 (51.6%) | 205/333 (61.6%) | 217/334 (65.0%) |
| Difference[a] % (two- sided 95% CI) | | 11.7% (5.3, 18.2) | |
| CMH test[b] p-value | | 0.0002 | |

BCVA=best corrected visual acuity, CI=confidence interval, CMH=Cochran-Mantel-Haenszel, ICE=intercurrent events, IRF=intraretinal fluid, LOCF=last observation carried forward, Num/Den=numerator/denominator, SAP=statistical analysis plan, SRF=subretinal fluid. LOCF method for the last available observed value prior to ICE was carried forward to impute missing data.
Intercurrent events (ICE) were handled according to primary estimand strategy for binary endpoints as described in Table 9-13 in Section 9.5 of the SAP.
[a]Difference is both 8 mg groups minus 2q8 and CI was calculated using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (< 60 vs. ≥ 60) and is displayed with two-sided 95% CIs.
[b]p-value for the one-sided Cochran-Mantel-Haenszel (CMH) test for superiority. Source: Table 14.2.2/1

**Reviewer's Comments:** *The Agency does not agree that "no IRF/SRF" represents a clinically significant benefit in visual function or is necessarily predictive of a visual function benefit.*

## Test decisions and statistical conclusions as per the G-SAP (full analysis set)

| Null hypothesis | p-value (one-sided test) | Estimate for Difference (two-sided 95% CI | Test decision $H_{x0}$ rejected |
|---|---|---|---|
| **Primary endpoint "Change from baseline in BCVA at Week 48": Non-inferiority** | | | |
| H10: non-inferiority of HDq12 vs. 2q8 in primary endpoint | p = 0.0009 | -0.97 (-2.87,0.92) letters [a] | Yes |
| H30: non-inferiority of HDq16 vs. 2q8 in primary endpoint | p = 0.0011 | -1.14 (-2.97,0.69) letters [a] | Yes |
| **Key secondary endpoint "Proportion of participants with no IRF and no SRF in central subfield at Week 16": Superiority** | | | |
| $H_{50}$: superiority of pooled high dose vs. 2q8 in key secondary endpoint | p = 0.0002 | 11.733% (5.263%, 18.204%) b | Yes |
| **Primary endpoint "Change from baseline in BCVA at Week 48": Superiority** | | | |
| $H_{60}$: superiority of HDq12 vs. 2q8 in primary endpoint | p = 0.8437 | -0.97 (-2.87,0.92) letters [a] | No, and hierarchical testing procedure stopped |
| $H_{80}$: superiority of HDq16 vs. 2q8 in primary endpoint | p = 0.8884 | -1.14 (-2.97,0.69) letters a | NA (test not performed because of failure above) |

BCVA=best corrected visual acuity, CI=Confidence limits, G-SAP=Global statistical analysis plan, IRF=Intraretinal fluid, MMRM=mixed model for repeated measurements, NA=not applicable, SRF=Subretinal fluid
[a]Estimate for contrast based on the MMRM model, computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively, with two-sided 95% CIs.
[b]Difference is HD groups minus 2q8 and CI was calculated using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (< 60 vs. ≥ 60) and is displayed with two-sided 95% Cis. Sources: Table 14.2.1/1 and Table 14.2.2/1

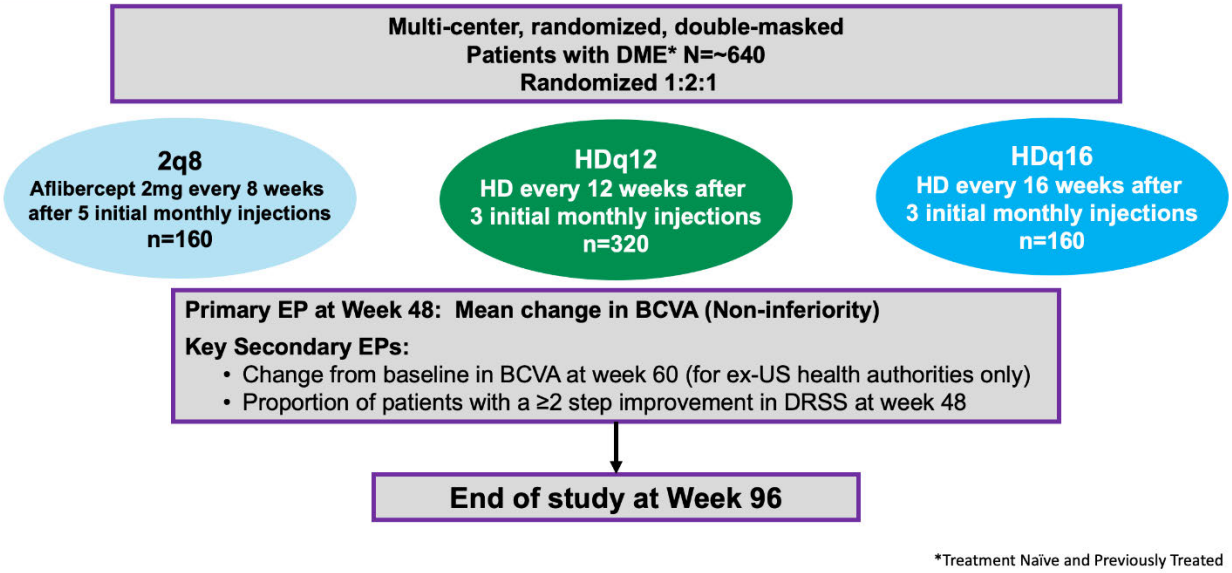
**Reviewer's Comments:** *No additional statistical testing beyond this point.*

**Study 3: Photon VGFTe-HD-DME-1934**

**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

**Trial Design:** Phase 3, multi-center, randomized, double-masked, active-controlled study of IVT administration of 8 mg aflibercept versus 2mg aflibercept in participants with Diabetic Macular Edema (DME). The study continues to Week 96. Data up to Week 48 have been submitted. The study is still ongoing.

## Study design overview




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.

## PHOTON: Dosing Schedule

| | Day 1 | Wk 4 | Wk 8 | Wk 12 | Wk 16 | Wk 20 | Wk 24* (1° Endpoint) | Wk 28 | Wk 32 | Wk 36 | Wk 40 | Wk 44 | Wk 48 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2q8 | X | X | X | X | X | o | X | o | X | o | X | o | X |
| HDq12 | X | X | X | o | o^ | X^ | o | o | X[a] | o | o | X[a] | o |
| HDq16 | X | X | X | o | o* | o* | X* | o | o | o | X[a] | o | o |

X=active injection
o=sham injections

***Dose Regimen Modifications in Year 1***
^Q12 group: If criteria are met, patients will continue q8.
*HDq16 group: If criteria are met at week 16 or 20, patient will continue q8. If criteria are met at week 24, patient will continue q12.
[a]For patients on a dosing interval of q12 or q16 weeks, DRM criteria will be assessed at dosing visits and if DRM criteria are met the next dosing interval will be reduced by 4 weeks.

| | Wk 52 | Wk 56 | Wk 60 | Wk 64 | Wk 68 | Wk 72 | Wk 76 | Wk 80 | Wk 84 | Wk 88 | Wk 92 | Wk 96 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2q8 | o | X | o | X | o | X | o | X | o | X | o | |
| HDq12 | o | X[a] | o | o | X[a] | o | o | X[a] | o | o | X[a] | |
| HDq16 | o | X[a] | o | o | o | X[a] | o | o | o | X[a] | o | |

***Dose Regimen Modifications in Year 2***
[a]Patients that continue on a dosing interval >8 weeks will be assessed at their dosing visits for DRM criteria for both shortening and extension of the interval by 4 week increments

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HD=high dose; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week

**Dose Regimen Modifications (DRM)/Rescue Regimen**

For masking purposes, assessments for dose regimen modifications (DRMs) were performed in all participants at all visits (through the interactive web response system [IWRS]) beginning at week 16. Based on these assessments, participants in the HD groups might have had their treatment intervals shortened (year 1 and year 2) or extended (year 2). The minimum interval between injections was 8 weeks which was considered a rescue regimen for patients randomized to HD aflibercept and unable to tolerate a dosing interval greater than every 8 weeks. **Participants in the aflibercept 2mg group remained on fixed q8 dosing throughout the study (i.e., did not have modifications of their treatment intervals regardless of the outcomes of the DRM assessments).**

During the first year, beginning at week 16, participants in the 8 mg groups had the dosing interval shortened (at the visits described below) if BOTH of the following criteria were met:

a. > 10 letter loss in BCVA from week 12 in association with persistent or worsening DME AND

b. > 50 µm increase in CRT from week 12

If a patient in the HDq12 group or the HDq16 group met both criteria at week 16 or week 20, the patient was dosed with 8 mg aflibercept at that visit and continued on a rescue regimen (aflibercept 8 mg, every 8 weeks). If a patient in the HDq16 group who had not met the criteria at week 16 or 20 met both criteria at week 24, the patient was dosed with 8 mg aflibercept at that visit and continued on q12 week dosing.

For patients whose interval was not shortened to q8 dosing at or before week 24, the interval was shortened if the DRM criteria were met at a subsequent dosing visit. Patients in the HDq12 group who met the criteria received the planned dose at that visit and then continued on a rescue regimen (aflibercept 8 mg, every 8 weeks). Patients in the HDq16 group who met these criteria received the planned dose at that visit and were to be continued on an every 12-week regimen if they were on a 16-week interval, or switched to the rescue regimen (aflibercept 8 mg, every 8 weeks) if they were

previously shortened to a 12-week interval. Therefore, a patient randomized to HDq16 whose injection interval had been shortened to q12 had their injection interval further shortened to q8 if these criteria were met at any subsequent dosing visit.

**Method of Treatment Assignment**

Approximately 640 patients will be randomized into 3 treatment groups in a ratio of 1:2:1 to receive either 2 mg aflibercept every 8 weeks following 5 initial monthly doses (2q8), HD every 12 weeks following 3 initial monthly doses (HDq12), or HD every 16 weeks following 3 initial monthly doses (HDq16), according to a central randomization scheme provided by an interactive web response system (IWRS) to the designated, unmasked investigator or study coordinator (or unmasked qualified designee). Randomization will be stratified according to baseline CRT (<400 μm, ≥400 μm), prior treatment for DME (yes, no) and geographic region (Rest of world, Japan).

## Statistical Plan

There were differing requirements for the submission to various global regulatory authorities. Two (2) different testing strategies were be described in the statistical analysis plan (SAP): a global plan (G-SAP), and a plan that specifically addresses requirements from EMA and PMDA (EP-SAP). The G-SAP will constitute the primary analysis for the study. The EP-SAP will be used for submission to the EMA/PMDA regulatory authorities.

The 2 primary hypotheses to be tested are the non-inferiority (NI) of HDq12 vs. 2q8 (control) and HDq16 vs. 2q8 (control) with respect to the primary endpoint of change from baseline in BCVA at week 48. The non-inferiority margin is set at 4 letters for each of the primary hypotheses. The key secondary analysis was based on the estimand concept, similar to the primary analysis. The key secondary efficacy endpoint (proportion of participants with ≥ 2-step improvement in DRSS at week 48) was analyzed using the Cochran-Mantel-Haenszel method, stratified by baseline CRT, prior DME treatment, and geographical region as specified for the primary endpoint. The key secondary hypotheses for non-inferiority (with a non-inferiority margin of 15%) were tested according to the hierarchical testing hierarchy, based on the 2-sided 95% CIs were reported. Non-inferiority was assessed by comparing the lower bound of the 95% CI for the estimated treatment difference with the non-inferiority margin.

**The Testing Order of Hierarchical Testing Procedure[a] in G-SAP and EP- SAP**

| G-SAP | EP-SAP |
|---|---|
| $H_{10}$: Q12 BCVA Week 48 non-inferiority | $H_{10}$: Q12 BCVA Week 48 non-inferiority |
| | $H_{20}$: Q12 BCVA Week 60 non-inferiority |
| $H_{30}$: Q16 BCVA Week 48 non-inferiority | $H_{30}$: Q16 BCVA Week 48 non-inferiority |
| | $H_{40}$: Q16 BCVA Week 60 non-inferiority |
| $H_{50}$: Q12 DRSS Week 48 non-inferiority | $H_{50}$: Q12 DRSS Week 48 non-inferiority |
| $H_{60}$: Q16 DRSS Week 48 non-inferiority | $H_{60}$: Q16 DRSS Week 48 non-inferiority |
| $H_{70}$: Q12 BCVA Week 48 superiority | $H_{70}$: Q12 BCVA Week 48 superiority |
| | $H_{80}$: Q12 BCVA Week 60 superiority |
| $H_{90}$: Q16 BCVA Week 48 superiority | $H_{90}$: Q16 BCVA Week 48 superiority |
| | $H_{100}$: Q16 BCVA Week 60 superiority |

[a] for comparisons with 2q8 study treatment group

**Disposition of Participants**

This study was conducted at 138 centers that randomized participants in Canada, Czech Republic, Germany, Hungary, Japan, United Kingdom, and the United States. A total of 970 participants were screened; 310 of them were screen failures with failure to meet inclusion/exclusion criteria being the most frequent reason for screen failure. Overall, 660 participants were randomized.

| | **2q8** | **8mg q12** | **8 mg q16** |
|---|---|---|---|
| | **(N=167)** | **(N=329)** | **(N=164)** |
| Number of patients who completed Week 48 | 157 (94%) | 300 (91%) | 156 (95%) |
| Number of patients who discontinued prior to Week 48 | 10 (6%) | 29 (9%) | 8 (5%) |
| Reasons for discontinuation prior to Week 48 | | | |
| Noncompliance with protocol by the subject | 1 (0.6%) | 0 | 0 |
| Adverse event | 0 | 4 (1%) | 1 (0.6%) |
| Decision by the investigator/sponsor | 0 | 4 (1%) | 1 (0.6%) |
| Withdrawal of consent by subject | 4 (2%) | 7 (2%) | 2 (1%) |
| Lost to follow-up | 1 (0.6%) | 5 (2%) | 1 (0.6%) |
| Death | 4 (2%) | 9 (3%) | 3 (2%) |

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; 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;
Source: PTT 14.1.1.3.

**Demographics and Baseline Characteristics (Full Analysis Set)**

| | **2q8** (N=167) | **HDq12** (N=328) | **HDq16** (N=163) |
|---|---|---|---|
| Age (years) Mean (SD) | 63.0 (9.8) | 62.1 (11.1) | 61.9 (9.5) |
| Age (years) Median | 64.0 | 63.0 | 62.0 |
| Age Q1: Q3 | 56.0: 70.0 | 55.0: 70.0 | 55.0: 68.0 |
| Age Min: Max | 38: 90 | 24: 87 | 37: 83 |
| Age category, n (%) <55 years | 29 (17.4%) | 77 (23.5%) | 38 (23.3%) |
| Age category, n (%) ≥55 - <65 years | 63 (37.7%) | 108 (32.9%) | 54 (33.1%) |
| Age category, n (%) ≥65 - <75 years | 54 (32.3%) | 107 (32.6%) | 57 (35.0%) |
| Age category, n (%) ≥75 years | 21 (12.6%) | 36 (11.0%) | 14 (8.6%) |
| Ethnicity, n (%) Hispanic or Latino | 31 (18.6%) | 54 (16.5%) | 34 (20.9%) |
| Not Hispanic or Latino | 133 (79.6%) | 266 (81.1%) | 126 (77.3%) |
| Not Reported | 3 (1.8%) | 8 (2.4%) | 3 (1.8%) |
| Race, n (%) American Indian or Alaska Native | 0 | 2 (0.6%) | 0 |

| | | | |
|---|---|---|---|
| Race, n (%) Asian | 30 (18.0%) | 48 (14.6%) | 23 (14.1%) |
| Race, n (%) Black or African American | 18 (10.8%) | 35 (10.7%) | 9 (5.5%) |
| Race, n (%) Native Hawaiian or Other Pacific Islander | 0 | 1 (0.3%) | 0 |
| Race, n (%) White | 112 (67.1%) | 231 (70.4%) | 128 (78.5%) |
| Race, n (%) Other | 0 | 1 (0.3%) | 0 |
| Race, n (%) Not Reported | 4 (2.4%) | 6 (1.8%) | 1 (0.6%) |
| Gender, n(%) Female | 75 (44.9%) | 118 (36.0%) | 64 (39.3%) |
| Gender, n(%) Male | 92 (55.1%) | 210 (64.0%) | 99 (60.7%) |
| Geographical region, n (%) Japan | 20 (12.0%) | 37 (11.3%) | 17 (10.4%) |
| Rest of World | 147 (88.0%) | 291 (88.7%) | 146 (89.6%) |
| Duration of diabetes (years): Mean (SD) | 15.9 (10.04) | 15.1 (9.96) | 15.7 (10.67) |
| Duration of diabetes (years): Median | 15.2 | 14.0 | 14.4 |
| Duration of diabetes (years): Q1: Q3 | 8.9: 21.0 | 7.2: 21.3 | 6.3: 22.1 |
| Duration of diabetes Min: Max | 1:61 | 0:51 | 0:54 |
| Diabetes type, n (%) Type I | 11 (6.6%) | 18 (5.5%) | 9 (5.5%) |
| Diabetes type, n (%) Type II | 156 (93.4%) | 310 (94.5%) | 154 (94.5%) |
| Insulin Dependent | 84 (50.3%) | 150 (45.7%) | 85 (52.1%) |
| Non-Insulin Dependent | 73 (43.7%) | 160 (48.8%) | 68 (41.7%) |
| NEI-VFQ-25 total score at baseline Mean (SD) | 76.7 (15.9) | 76.8 (17.3) | 77.9 (15.6) |
| BCVA (ETDRS letter score) Mean (SD) | 61.5 (11.22) | 63.6 (10.10) | 61.4 (11.76) |
| BCVA (ETDRS letter score) Median | 63.0 | 65.0 | 64.0 |
| BCVA (ETDRS letter score) Q1: Q3 | 54.0: 70.0 | 57.0: 72.0 | 55.0: 71.0 |
| BCVA (ETDRS letter score) Min: Max | 24: 78 | 27: 79 | 29: 78 |
| Baseline BCVA category ≤73 letters | 147 (88.0%) | 269 (82.0%) | 140 (85.9%) |
| Baseline BCVA category >73 letters | 20 (12.0%) | 59 (18.0%) | 23 (14.1%) |
| CRT (microns) Mean (SD) | 457.2 (144.0) | 449.1 (127.4) | 460.3 (117.8) |
| CRT Median | 417.0 | 431.0 | 432.0 |
| CRT Q1 : Q3 | 346.0: 532.0 | 359.0: 518.0 | 371.0: 540.0 |
| CRT Min: Max | 260: 1014 | 229: 1309 | 255: 926 |
| CRT Missing | 0 | 1 | 0 |
| CRT category per reading center[a] <400 microns | 72 (43.1%) | 134 (40.9%) | 65 (39.9%) |
| CRT category per reading center[a] ≥400 microns | 95 (56.9%) | 194 (59.1%) | 98 (60.1%) |
| CRT category per IWRS[b] (used for stratification) <400 microns | 69 (41.3%) | 138 (42.1%) | 69 (42.3%) |
| CRT category per IWRS[b] (used for stratification) ≥400 microns | 98 (58.7%) | 190 (57.9%) | 94 (57.7%) |
| Intraocular Pressure Mean (SD) | 15.9 (2.99) | 15.3 (3.24) | 14.9 (3.25) |
| Intraocular Pressure Median | 16.0 | 15.0 | 15.0 |
| Intraocular Pressure Q1: Q3 | 14.0: 18.0 | 13.0: 18.0 | 13.0: 17.0 |
| Intraocular Pressure Min: Max | 8: 23 | 8: 24 | 7: 24 |
| Diabetic Retinopathy Severity Score (DRSS) 10 | 0 | 1 (0.3%) | 2 (1.2%) |
| Diabetic Retinopathy Severity Score (DRSS) 12 | 0 | 2 (0.6%) | 0 |
| Diabetic Retinopathy Severity Score (DRSS) 14 | 1 (0.6%) | 1 (0.3%) | 1 (0.6%) |
| Diabetic Retinopathy Severity Score (DRSS) 15 | 1 (0.6%) | 0 | 0 |
| Diabetic Retinopathy Severity Score (DRSS) 20 | 3 (1.8%) | 13 (4.0%) | 2 (1.2%) |
| Diabetic Retinopathy Severity Score (DRSS) 35 | 66 (39.5%) | 121 (36.9%) | 66 (40.5%) |
| Diabetic Retinopathy Severity Score (DRSS) 43 | 34 (20.4%) | 59 (18.0%) | 36 (22.1%) |
| Diabetic Retinopathy Severity Score (DRSS) 47 | 17 (10.2%) | 46 (14.0%) | 15 (9.2%) |
| Diabetic Retinopathy Severity Score (DRSS) 53 | 22 (13.2%) | 34 (10.4%) | 11 (6.7%) |
| Diabetic Retinopathy Severity Score (DRSS) 61 | 9 (5.4%) | 20 (6.1%) | 9 (5.5%) |
| Diabetic Retinopathy Severity Score (DRSS) 65 | 4 (2.4%) | 11 (3.4%) | 9 (5.5%) |
| Diabetic Retinopathy Severity Score (DRSS) 71 | 1 (0.6%) | 1 (0.3%) | 2 (1.2%) |
| Diabetic Retinopathy Severity Score (DRSS) 75 | 0 | 1 (0.3%) | 0 |
| Diabetic Retinopathy Severity Score (DRSS) 90 (non-gradable) | 9 (5.4%) | 18 (5.5%) | 10 (6.1%) |

Abbreviations: 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; 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; CRT=central retinal thickness; DME=Diabetic macular edema; DRSS=Diabetic Retinopathy Severity Score; EDC=electronic data capture; ETDRS=early treatment diabetic retinopathy study; HD=high dose; IWRS=interactive web response system; max=maximum; min=minimum;

n=number; Q=quartile; SD=standard deviation.
[a]Baseline values; used for subgroup analyses
[b]Reflects site's entry of reading center values from screening visit into IWRS; 10 patients were stratified incorrectly, based on incorrect data entry in IWRS.
[c]Used for subgroup analyses
[d]Reflects entry of prior DME treatment information by site into IWRS; 47 patients had data entered inconsistently between IWRS and EDC.
Source: PTT 14.1.2.3

## Summary of Treatment Exposure in Study Eye through Week 48 (Photon Safety Analysis Set)

| | **2q8** (N=167) | **HDq12** (N=328) | **HDq16** (N=163) |
|---|---|---|---|
| Total number of active injections | 1292 | 1875 | 806 |
| Total number of sham injections | 580 | 1720 | 1054 |
| 1 active injection per patient, n (%) | 2 (1.2%) | 2 (0.6%) | 1 (0.6%) |
| 2 active injections per patient, n (%) | 0 | 7 (2.1%) | 1 (0.6%) |
| 3 active injections per patient, n (%) | 0 | 11 (3.4%) | 3 (1.8%) |
| 4 active injections per patient, n (%) | 2 (1.2%) | 11 (3.4%) | 6 (3.7%) |
| 5 active injections per patient, n (%) | 2 (1.2%) | 12 (3.7%) | 146 (89.6%) |
| 6 active injections per patient, n (%) | 3 (1.8%) | 273 (83.2%) | 2 (1.2%) |
| 7 active injections per patient, n (%) | 10 (6.0%) | 12 (3.7%) | 4 (2.5%) |
| 8 active injections per patient, n (%) | 148 (88.6%) | 0 | 0 |
| Mean number of injections (SD) | 7.7 (0.98) | 5.7 (0.96) | 4.9 (0.61) |
| Median number of injections | 8.0 | 6.0 | 5.0 |
| Q1: Q3 | 8.0: 8.0 | 6.0: 6.0 | 5.0: 5.0 |
| Min: Max | 1: 8 | 1: 7 | 1: 7 |

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; 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; The percentage was based on the number of patients in each treatment group as a denominator. Study drugs given at week 48 or beyond were not included in this table. Patients in the HD groups could have had their interval shortened if protocol specified criteria were met. Source: PTT 14.1.4.1

**Summary of Treatment Exposure in the Study Eye Through Week 48**

| | 2q8 (N=157) | HDq12 (N=300) | HDq16 (N=156) |
|---|---|---|---|
| Patients maintained with q12 or longer dosing interval, n (%) | NA | 273 (91.0%) | 150 (96.2%) |
| Patients maintained with q16 dosing interval, n (%) | NA | NA | 139 (89.1%) |
| Patients with q12 or longer dosing interval as the last[a] intended dosing interval, n (%) | NA | 262 (87.3%) | 146 (93.6%) |
| Patients with q16 dosing interval as the last[a] intended dosing interval, n (%) | NA | NA | 136 (87.2%) |
| Patients shortened to q8 dosing interval at week 16, n (%) | NA | 3 (1.0%) | 1 (0.6%) |
| Patients shortened to q8 dosing interval at week 20, n (%) | NA | 12 (4.0%) | 3 (1.9%) |
| Patients with a shortened dosing interval anytime, n (%) | NA | 27 (9.0%) | 17 (10.9%) |
| Patients with a shortened dosing interval to q8 anytime, n (%) | NA | 27 (9.0%) | 6 (3.8%) |
| Patients with a shortened dosing interval to q12 anytime [b], n (%) | NA | NA | 13 (8.3%) |

Abbreviations: NA=Not applicable; 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; 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; All HD= / indicates categories that did not apply. [a] Refers to the patient's assigned interval at week 48. [b] Includes participants who were only shortened to q12 as well as participants who were shortened to q12 and further shortened to q8. Source: PTT 14.1.4.2

**Primary Endpoint -- Change from Baseline in BCVA (ETDRS Letters) at Week 48 in the Study Eye, MMRM (Full Analysis Set)**

| Treatment | LS Mean (SE) change from BL | Mean (SD) change from BL | BL Mean | Number of patients with Week 48 data | DF | Difference [a] | t- value | 1-sided NI p-value [b] | 1-sided superiority p-value | Estimate for difference and 2-sided 95% CI [c] |
|---|---|---|---|---|---|---|---|---|---|---|
| HDq12 (N=328) | 8.10 (0.61) | 8.77 (8.95) | 63.6 | 277 | 351.5 | HDq12-2q8 | 3.9881 | <0.0001 | 0.7447 | -0.57 (-2.26, 1.13) |
| HDq16 (N=163) | 7.23 (0.71) | 7.86 (8.38) | 61.4 | 149 | 315.0 | HDq16-2q8 | 2.7533 | 0.0031 | 0.9388 | -1.44 (-3.27, 0.39) |
| 2q8 (N=167) | 8.67 (0.73) | 9.21 (8.99) | 61.5 | 150 | | | | | | |

Abbreviations: 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; 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; DF=degrees of freedom; NI=non-inferiority; LS=least square; SE=standard error; SD=standard deviation

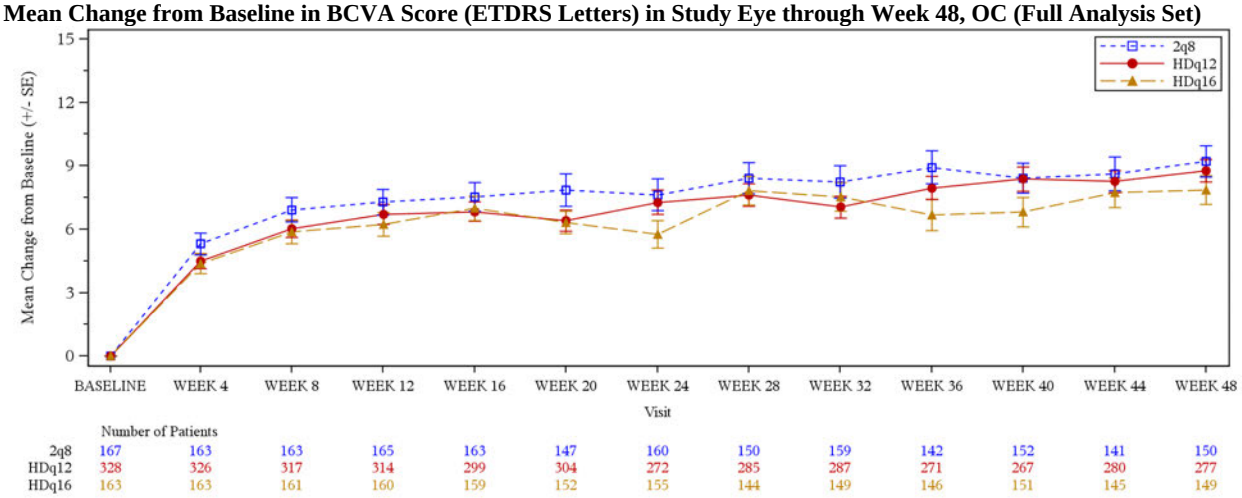
A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT (from reading center) [<400µm vs. ≥400µm], prior treatment for DME (per EDC; [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1).

[a] The contrast also included the interaction term for treatment x visit.

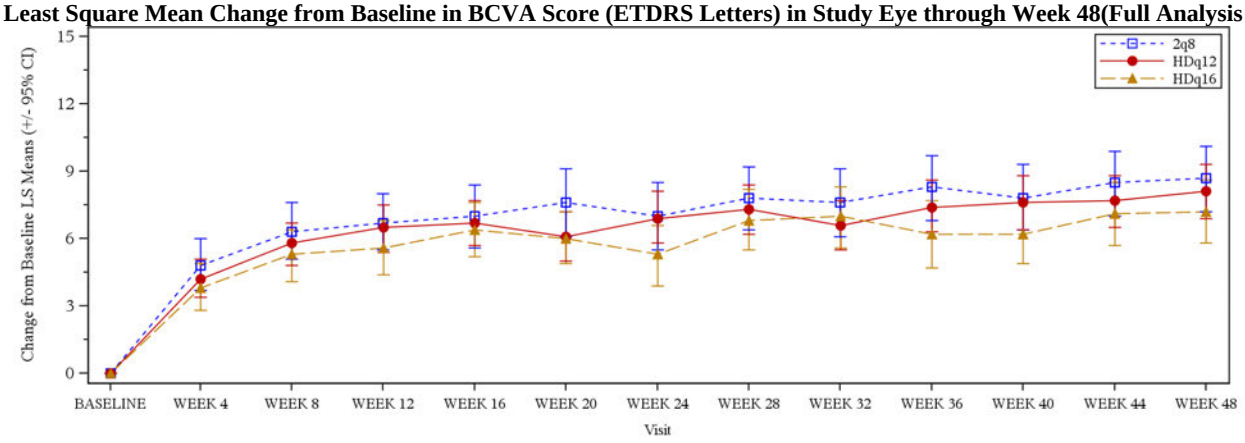
[b] p-value for the one-sided non-inferiority (NI) test at a margin of 4 letters.

[c] Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs. Source: PTT 14.2.1.1

**Mean Change from Baseline in BCVA Score (ETDRS Letters) in Study Eye through Week 48, OC (Full Analysis Set)**




**Least Square Mean Change from Baseline in BCVA Score (ETDRS Letters) in Study Eye through Week 48(Full Analysis Set)**




## Key Secondary Endpoint – Proportion of Participants with a ≥ 2-Step Improvement from Baseline in DRSS at Week 48 (LOCF) (Full Analysis Set)

| | Patients with a ≥ 2-step Improvement | Adjusted Difference (%) |
|---|---|---|
| **Treatment** | **From Baseline in DRSS, n (%)** | **2-sided (95% CI) [a]** |
| HDq12 (N=328) | 90/310 (29.0%) | 1.98 ( -6.61, 10.57) |
| HDq16 (N=163) | 30/153 (19.6%) | -7.52 ( -16.88, 1.84) |
| 2q8 (N=167) | 42/158 (26.6%) | |

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; 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.
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1). LOCF= the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data. Patients were considered as non-responders if all post-baseline measurements were missing or non-gradable.
[a] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400 µm, ≥400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]). The non-inferiority margin was set at 15%. Missing or ungradable baseline was not included in the denominator. PTT 14.2.2.1

**Test Decisions and Statistical Conclusions for Global Analysis (Full Analysis Set)**

| Null hypothesis | p-value (one-sided) | Two-sided 95% CI | Test decision |
|---|---|---|---|
| Primary endpoint "Change from baseline in BCVA at Week 48" | | | |
| H10: non-inferiority of HDq12 vs. 2q8 in primary endpoint | $p < 0.0001$ | -2.26, 1.13 | Yes |
| H30: non-inferiority of HDq16 vs. 2q8 in primary endpoint | $p = 0.0031$ | -3.27, 0.39 | Yes |
| Key Secondary endpoint "Proportion of patients with a ≥2-step improvement in DRSS score" | | | |
| H50: non-inferiority of HDq12 vs. 2q8 in key secondary endpoint | NA | -6.61, 10.57 | Yes |
| H60: non-inferiority of HDq16 vs. 2q8 in key secondary endpoint | NA | -16.88, 1.84 | No, and hierarchical testing procedure stopped |
| Primary endpoint "Change from baseline in BCVA at Week 48" | | | |
| H70: superiority of HDq12 vs. 2q8 in primary endpoint | NA | | NA |
| H90: superiority of HDq16 vs. 2q8 in primary Endpoint | NA | | NA |

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; 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; CI=confidence interval; DRSS=Diabetic Retinopathy Severity Scale; NA= not applicable Source: PTT 14.2.1.1 and PTT 14.2.2.1

## 6.1. Statistical Review

**Extracted from the Statistical Review by Juan C. Vivar, Ph.D. and Solomon Chefo, Ph.D., Team Leader**

nAMD Indication

Although the total study duration is 96 weeks, efficacy and safety support in this BLA was based on the first 48 weeks of data. The main efficacy evaluation was based on BCVA assessed every 4 weeks through Week 96 as measured by the number of letters read at a starting distance of 4 meters (range: 0-100 letters). The primary efficacy endpoint was the change in BCVA from baseline at Week 48. The primary efficacy analysis was an evaluation of noninferiority of HDq12 or HDq16 to 2q8 in the primary efficacy endpoint on the full analysis set (FAS), including all randomized subjects who received at least one dose of study medication (see more details on the data handling approaches in Section 3.2.1.2). The noninferiority margin was set at -4.0 letters.

The treatment groups in PULSAR study were well balanced with respect to the demographic and baseline characteristics, in general. During the first 48 weeks of treatment, about 7% of subjects discontinued from the study and the discontinuation rates were comparable across the treatment groups.

In PULSAR study, both HDq12 and HDq16 treated subjects had a noninferior mean change in BCVA from baseline at Week 48 compared to 2q8 treated subjects. The adjusted mean change in BCVA from baseline at Week 48 was +6.1 letters in the HDq12 group, +5.9 letters in the HDq16 group, and +7.0 letters in the 2q8 group with treatment differences of -1.0 (95% CI: -2.9 to 0.9) for HDq12 vs. 2q8 and -1.1 (95% CI: -3.0 to 0.7) for HDq16 vs. 2q8. Although noninferiority in the primary endpoint was

established in the study, because of the frequent dosing, subjects that received aflibercept 2q8 displayed a numerical advantage in the BCVA gain from baseline through Week 48 compared to subjects that received the high dose of aflibercept.

**Adjusted Mean Change in BCVA from Baseline at Week 48 (FAS) (PULSAR)**

| Analysis Visit | | 2q8 (N = 336) | HDq12 (N = 335) | HDq16 (N = 338) |
|---|---|---|---|---|
| Baseline | Mean (SD) | 59.0 (14.01) | 59.8 (13.42) | 60.1 (12.40) |
| Week 48 | LS Mean (95% CI) | 7.0 (5.6, 8.5) | 6.1 (4.5, 7.6) | 5.9 (4.5, 7.3) |
| | Diff (95% CI) | --- | -1.0 (-2.9, 0.9) | -1.1 (-3.0, 0.7) |

Note: Adjusted mean changes in each treatment group and treatment differences (95% CI estimates) were based on MMRM method using FAS (See Section 3.2.1.2 for details).

Sensitivity and supplementary analyses performed under different data handling strategies for missing data (including tipping point analysis) and intercurrent events were consistent with the primary efficacy results, leading to the same conclusion for a robust interpretation of the noninferiority findings.

Additionally, PULSAR study results for the proportion of subjects who had no retinal fluid at Week 16 established superiority of the pooled HD groups compared to 2q8 group. For example, at Week 16, 63% of subjects in the pooled HD groups had no retinal fluid compared to 52% of subjects in the 2q8 group with a treatment difference of 12% (95% CI: 5%, 18%). Although superiority was established at Week 16, the efficacy results were not consistent throughout the study. This was likely because treatment groups had variable dosing intervals after Week 16 and an increasing number of subjects in each treatment group exhibited fluid dryness in the immediate visit after injection was received. Thus, the clinical benefit of HD of aflibercept in retinal fluid dryness compared to 2q8 is questionable. The reviewer defers to the clinical review team for the clinical meaningfulness of this endpoint.

In summary, based on the collective efficacy evidence from the adequate and well controlled trial of PULSAR study, the reviewer concludes that the application for the nAMD indication provided substantial evidence for comparable efficacy benefit (BCVA gain) of aflibercept 8 mg administered every 12 weeks and every 16 weeks after three initial monthly doses compared to aflibercept 2 mg administered every 8 weeks after three initial monthly doses. However, the study did not establish consistent treatment benefit of the high doses of aflibercept in retinal fluid dryness compared to the active control.

DME/DR Indications

Although the total study duration is 96 weeks, efficacy and safety support in this BLA was based on the first 48 weeks of data. The main efficacy evaluation was based on BCVA assessed every 4 weeks through Week 96 as measured by the number of letters read at a starting distance of 4 meters (range: 0-100 letters) and based on diabetic retinopathy severity as measured by the diabetic retinopathy severity score (DRSS).

The primary efficacy endpoint was the change in BCVA from baseline at Week 48. The primary efficacy analysis was an evaluation of noninferiority of HDq12 or HDq16 to 2q8 in the primary efficacy endpoint on the full analysis set (FAS), including all randomized subjects who received at

least one dose of study medication (See more details in Section 3.2.2.2). The noninferiority margin was set at -4.0 letters.

The key secondary efficacy endpoint was the proportion of subjects with a ≥ 2-step improvement in DRSS at Week 48. This endpoint is intended to support the DR indication. The secondary efficacy analysis was an evaluation of noninferiority of each high dose group compared to the 2q8 group in the key secondary efficacy endpoint on the FAS. The noninferiority margin was set at -10%. Noninferiority in the key secondary endpoint was tested if noninferiority of both HDq12 and HDq16 to 2q8 in the primary endpoint was established.

The treatment groups in the PHOTON study were well balanced with respect to the demographic and baseline characteristics, in general (Table 18). During the first 48 weeks of treatment, about 7% of subjects discontinued from the study and discontinuation rates were comparable across the treatment groups (Table 16).

In PHOTON study, both HDq12 and HDq16 treated subjects had a noninferior mean change in BCVA from baseline at Week 48 compared to 2q8 treated subjects (Table 2). As shown, the adjusted mean change in BCVA from baseline at Week 48 was +8.1 letters in the HDq12 group, +7.2 letters in the HDq16 group, and +8.7 letters in the 2q8 group with treatment differences of -0.6 (95% CI: -2.3 to 1.1) for HDq12 vs. 2q8 and -1.4 (95% CI: -3.3 to 0.4) for HDq16 vs. 2q8. Although noninferiority in the primary endpoint was established in the study, because of the relatively frequent dosing, subjects that received aflibercept 2q8 displayed a numerical advantage in the BCVA gain from baseline through Week 48 compared to subjects that received either high dose of aflibercept (Figure 9).

**Adjusted Mean Change in BCVA from Baseline at Week 48 (FAS) (PHOTON)**

| Analysis Visit | | 2q8 (N = 167) | HDq12 (N = 328) | HDq16 (N = 163) |
|---|---|---|---|---|
| Baseline | Mean (SD) | 61.5 (11.22) | 63.6 (10.10) | 61.4 (11.76) |
| Week 48 | LS Mean (95% CI) | 8.7 (7.2, 10.1) | 8.1 (6.9, 9.3) | 7.2 (5.8, 8.6) |
| | Diff (95% CI) | --- | -0.6 (-2.3, 1.1) | -1.4 (-3.3, 0.4) |

Note: Adjusted mean changes in each treatment group and treatment differences (95% CI estimates) were based on MMRM method using FAS (See Section 3.2.2.2 for details).

Sensitivity and supplementary analyses performed under different data handling strategies for missing data and intercurrent events were consistent with the primary efficacy results, leading to the same conclusion for a robust interpretation of the noninferiority findings (Table 22).

Additionally, PHOTON study results for the key secondary endpoint of the proportion of subjects who achieved ≥ 2-step improvement in DRSS at Week 48 established noninferiority of HDq12 to 2q8 but not HDq16 to 2q8 using a noninferiority margin of -10% (Table 24). For example, at Week 48, 27%, 29%, and 20% of subjects in the 2q8, HDq12, and HDq16 treatment groups, respectively, achieved ≥ 2-step improvement in DRSS from baseline to Week 48 with adjusted treatment differences of 2.0% (95% CI: -6.4%, 10.4%) for HDq12 versus 2q8 and -7.5% (95% CI: -16.8%, 1.8%) for HDq16 versus 2q8.

In summary, based on the collective efficacy evidence from the adequate and well controlled trial of PHOTON study, the reviewer concludes that the application for the DME indication provided substantial evidence for comparable efficacy benefit (in BCVA gain) of aflibercept 8 mg administered every 12 weeks and every 16 weeks after three initial monthly doses compared to aflibercept 2 mg administered every 8 weeks after five initial monthly doses.

For the DR indication, the application provided evidence for comparable efficacy benefit of aflibercept 8 mg administered every 12 weeks after three initial monthly doses compared to aflibercept 2 mg administered every 8 weeks after five initial doses. For this indication, the application did not provide evidence of comparable efficacy benefit of aflibercept 8 mg administered every 16 weeks after three initial doses compared to aflibercept 2 mg administered every 8 weeks after five initial doses.

# 7. Review of Safety

## 7.1. Deaths

**Candela**

There were no deaths during this study.

**Pulsar**

| Actual Treatment group | Subject identifier | Age/Sex/Race/ Study eye | Category/Location/Laterality | Study drug start date/Stop date | Date of death | AE (MedDRA preferred term) with fatal outcome | Start/Stop (relative to treatment) |
|---|---|---|---|---|---|---|---|
| 2q8 | (b) (6) | 96/F/W/L | Gastrointestinal/Abdominal Cavity/Other | (b) (6) | (b) (6) | Abdominal strangulated hernia | (b) (6) |
| 2q8 | | 83/M/A/L | Other/Lung/Right | | | Pneumonia aspiration | |
| 2q8 | | 83/M/W/L | Myocardial Infarction/Heart/Other | | | Cardiac arrest | |
| 2q8 | | 89/M/W/R | Symptomatic Skeletal Event/Skull/Other | | | Skull fracture | |
| 2q8 | | 69/M/W/L | Stroke/Cerebral Artery/Right | | | Cerebral infarction | |
| HDq12 | | 87/M/W/L | Immune-Related/Lung/Other | | | COVID-19 pneumonia | |
| HDq12 | | 81/F/W/R | Skeletal Related Event/Back/Left | | | Non-small cell lung cancer | |
| HDq12 | | 83/F/W/R | Tumor Lysis Syndrome/Liver Fissure/Other | | | Metastatic neoplasm | |
| HDq16 | | 91/F/W/R | Other/Unknown/Other | | | Death | |

AE Adverse event. MedDRA Medical Dictionary for Regulatory Activities. SOC System Organ Class. Race: A = Asian B = Black W = White AI = American Indian or Alaska Native NH = Native Hawaiian or Other Pacific Islander NR = Not Reported MUL=Multiple. Sex: F = female, M = male. Study eye: L = left, R = right; Relative to treatment start = date of death minus date of first study drug administration plus 1 day. Relative to treatment stop = date of death minus date of last study drug administration. 2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals. 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. MedDRA version 25.0. program location:/unblinded/bayer245919/stats/week48/primary/prog/listings/l_14_3_2_death.sas/15DEC2022/11:18

**Photon**

| Group | Patient ID | Age/Sex /Race | Date of First Treatment | Date of Last Treatment | Last Scheduled Visit | Last Scheduled Visit Date | Reason for Death/Date of Death |
|---|---|---|---|---|---|---|---|
| 2q8 | (b) (6) | 80/F/W | (b) (6) | (b) (6) | Week 16 | (b) (6) | Died of unspecified infection in Nursing Home/ (b) (6) |
| 2q8 | | 60/M/W | | | Week 32 | | Unknown/ (b) (6) |
| 2q8 | | 73/M/W | | | Week 36 | | Myocardial Infarction (b) (6) |
| 2q8 | | 60/M/W | | | Week 44 | | Cardiac Arrest/ (b) (6) |
| HDq12 | | 54/M/O | | | Week 36 | | Unknown (b) (6) |
| HDq12 | | 63/M/W | | | Week 12 | | Site was called on (b) (6) |
| HDq12 | | 70/M/W | | | Week 4 | | Cardiac Arrest due to Pneumoperitone UM suspected perforated duodenal ulcer (b) (6) |
| HDq12 | | 82/M/W | | | Week 4 | | Unknown (b) (6) |
| HDq12 | | 69/F/W | | | Week 4 | | Heart Attack (b) (6) |
| HDq12 | | 43/M/O | | | Week 32 | | Pneumonia/ (b) (6) |
| HDq12 | | 55/F/B | | | Week 16 | | Cardiac Arres (b) (6) |
| HDq12 | | 82/F/W | | | Week 32 | | Unknown (b) (6) |
| HDq12 | | 70/F/B | | | Week 32 | | Ovarian Cancer/ (b) (6) |
| HDq16 | | 68/M/W | | | Week 40 | | Multiorgan Failur (b) (6) |
| HDq16 | | 65/M/W | | | Week 16 | | Unknown (b) (6) |
| HDq16 | | 51/M/W | | | Week 4 | | Chronic Respiratory Failure (b) (6) |

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; 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. A=Asian, B=Black or African American, W=White, AI=American Indian or Alaska Native, NH=Native Hawaiian or other Pacific Islander, MU=Multiple; Date of first treatment=the date of the first study eye injection; Date of last treatment=the date of last administration of study medication (active [including rescue], sham, or fellow eye treatment)
/sasdata/Data/Production/BDM/VGFT/VGFT-HD-DME/VGFTe-DME-1934/Week48/Analysis_CSR/Programs/TFL/Generated/l_disc_16_2_1_2.sas (b) (6) 28OCT2022 10:39 SAS Linux 9.4)

## 7.2. Summary of Ocular Treatment-Emergent Adverse Events in the Study

| Adverse Reactions | PULSAR | | | PHOTON | | |
|---|---|---|---|---|---|---|
| | EYLEA HD q12 | EYLEA HD q16 | EYLEA 2q8 | EYLEA HD q12 | EYLEA HD q16 | EYLEA 2q8 |
| | n=335 | n=338 | n=336 | n=328 | n=163 | n=167 |
| Cataract[a] | 4% | 4% | 4% | 3% | 6% | 3% |
| Conjunctival hemorrhage[a] | 3% | 2% | 1% | 4% | 4% | 4% |
| Intraocular pressure increased[a] | 4% | 4% | 2% | 3% | 1% | 4% |
| Ocular discomfort/eye pain/eye irritation[a] | 3% | 3% | 2% | 4% | 2% | 4% |
| Vision blurred[a] | 4% | 6% | 7% | 3% | 3% | 4% |
| Vitreous floaters[a] | 1% | 4% | 3% | 5% | 2% | 3% |
| Vitreous detachment[a] | 2% | 3% | 2% | 4% | 2% | 1% |
| Corneal epithelium defect[a] | 2% | 2% | 3% | 3% | 6% | 1% |
| Retinal hemorrhage | 3% | 3% | 4% | 0 | 4% | 1% |
| Intraocular inflammation[a] | 1% | 1% | 1% | 1% | 0 | 1% |
| Retinal pigment epithelial tear/epitheliopathy[a] | 2% | 1% | 2% | <1% | 0 | 0 |
| Vitreous hemorrhage | <1% | 1% | 1% | 2% | 1% | 1% |
| Retinal Detachment[a] | 1% | <1% | 0 | <1% | 1% | 0 |
| Foreign body sensation in eyes[a] | 1% | 1% | 2% | <1% | 0 | 0 |
| Retinal pigment epithelial detachment[a] | 1% | 1% | 2% | 0 | 0 | 0 |

[a]Includes related terms

## 7.3. Immunogenicity

Immunogenicity was analyzed in the PULSAR and PHOTON studies using the Anti-drug antibody (ADA) analysis set and neutralizing anti-drug antibody (Nab) analysis set. The ADA analysis set included all participants who received study treatment and had at least 1 non-missing result in the ADA assay following the first study dose. The NAb analysis set included all participants who received any study treatment and were included in the ADA analysis set, tested negative at all ADA sampling times or tested positive at one or more post-dose ADA sampling times, and had at least one non-missing post-dose Nab result (either imputed or analysis result).

In the PULSAR study, the samples were taken at baseline and Week 48 visit. Treatment-emergent ADA responses were observed in 24 out of 793 participants at all dose levels. The incidence of treatment-emergent ADA in 2q8, HDq12, and HDq16 treatment groups during the 48-week period of treatment with intravitreally administrated aflibercept was 4/260 (1.5%), 11/269 (4.1%) and 9/264 (3.4%), respectively (Table 38 AMD). In each group the titers were low (<1000). None of the samples positive in the ADA assay demonstrated neutralizing activity. The safety profile of participants 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 participants with positive ADAs. Overall, no relevant impact of treatment-emergent ADAs on the safety profile could be observed (Module 5.3.5.1, PULSAR W48 CSR, Listings 16.2.7/3 and 16.2.8.1/5).

AMD: Number of participants with anti-drug antibodies to aflibercept at Week 48 (PULSAR, ADA analysis set)

| Category | 2q8 | HDq12 | HDq16 |
|---|---|---|---|
| | N=260 (100%) | N=269 (100%) | N=264 (100%) |
| ADA analysis set | 260 (100%) | 269 (100%) | 264 (100%) |
| Negative (a) | 249 (95.8%) | 250 (92.9%) | 250 (94.7%) |
| Pre-existing immunoreactivity (b) | 7 (2.7%) | 7 (2.6%) | 4 (1.5%) |
| Treatment-boosted (c) | 0 | 0 | 0 |
| Treatment-emergent positive (d) | 4 (1.5%) | 11 (4.1%) | 9 (3.4%) |
| Missing | 0 | 1 (0.4%) | 1 (0.4%) |
| Persistent | 0 | 0 | 0 |
| Indeterminate | 4 (1.5%) | 11 (4.1%) | 9 (3.4%) |
| Transient TE and TB Maximum Titer Category | 0 | 0 | 0 |
| Low (< 1000) | 4 | 11 | 9 |
| Moderate (1000-10000) | 0 | 0 | 0 |
| High (> 10000) | 0 | 0 | 0 |
| NAb Analysis Set | 256 (98.5%) | 267 (99.3%) | 263 (99.6%) |
| NAb Negative | 256 (98.5%) | 267 (99.3%) | 263 (99.6%) |
| NAb Positive | 0 | 0 | 0 |

ADA = anti-drug antibody, Nab = neutralizing anti-drug antibody, TB = treatment-boosted, TE = treatment- emergent
See Definitions of terms for treatment arms description.

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 level
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.

Note: Percentages are based on ADA analysis set.
Source: Module 5.3.5.1, PULSAR W48 CSR, Tables 14.3.7/22, 14.3.7/23 and 14.3.7/24

In Photon, the incidence of treatment-emergent ADA in the 2q8, HDq12, and HDq16 treatment groups during the 48-week period of treatment with intravitreally administered aflibercept was 0/137 (0%), 3/263 (1.1%) and 2/141 (1.4%), respectively. No treatment-boosted (TB) 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 24 DME). The systemic safety profile of patients with treatment-emergent or pre-existing ADAs was reviewed for reactions potentially related to immunogenicity such as hypersensitivity, rash, pruritus, and urticaria. No such adverse events were reported in patients with positive ADAs. Overall, no relevant impact of treatment- emergent ADAs on the safety profile could be observed.

DME: Summary of ADA status, ADA category, maximum titer category, and NAb status by treatment group in participants with DME (PHOTON, ADA analysis set)

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

ADA = anti-drug antibody; n = Number of participants; NAb = neutralizing antibody; TE = Treatment-emergent; TB = Treatment-boosted; DME = Diabetic macular edema; Note: Percentages are based on ADA analysis set.
Source: Module 5.3.5.1, PHOTON W48 CSR, Appendix 16.1.14 CP Report, Table 10

## 8. Financial Disclosure

**Covered Clinical Study (Name and/or Number): Candela, Pulsar and Photon**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: >7500 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 55 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 50<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator in: 5<br>Sponsor of covered study: 0 | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☒ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☒ | No ☐ (Request explanation from Applicant) |

## 9. Systemic Blood Levels

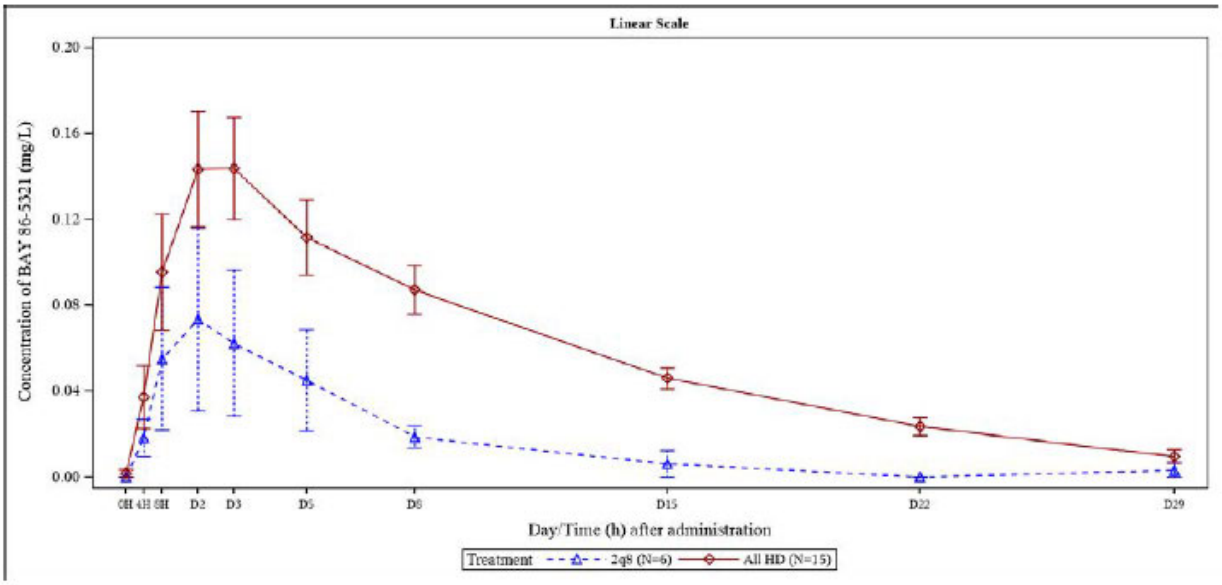
| | | | | Free aflibercept | | |
|---|---|---|---|---|---|---|
| **Treatment** | **Time** | **n total** | **n ≥ LLOQ** | **Geom. Mean ± SD** | **Arithm. Mean ± SD** | **Median** |
| 2q8 (N = 6) | Day 1, Pre-dose | 4 | 0 | N.C | 0.00 (0.00) | 0.00 |
| 2q8 (N = 6) | Day 1, 4 Hours Post-dose | 6 | 3 | N.C | 0.0182 (0.0210) | 0.0127 |
| 2q8 (N = 6) | Day 1, 8 Hours Post-dose | 5 | 4 | 0.03 (3.31) | 0.0549 (0.0742) | 0.0282 |
| 2q8 (N = 6) | Day 2 | 6 | 6 | 0.04 (2.68) | 0.0734 (0.105) | 0.0357 |
| 2q8 (N = 6) | Day 3 | 6 | 6 | 0.04 (2.49) | 0.0622 (0.0835) | 0.0320 |
| 2q8 (N = 6) | Day 5 | 6 | 5 | 0.03 (2.67) | 0.0451 (0.0580) | 0.0283 |
| 2q8 (N = 6) | Day 8 | 5 | 4 | 0.02 (1.66) | 0.0187 (0.0110) | 0.0212 |
| 2q8 (N = 6) | Day 15 | 5 | 1 | N.C | 0.00624 (0.0140) | 0.00 |
| 2q8 (N = 6) | Day 22 | 5 | 0 | N.C | 0.00 (0.00) | 0.00 |
| 2q8 (N = 6) | Day 29 | 5 | 1 | N.C | 0.00330 (0.00738) | 0.00 |
| HDq12 +HDq16 (n=13) | Day 1, Pre-dose | 12 | 0 | N.C | 0.00 (0.00) | 0.00 |
| HDq12 +HDq16 (n=13) | Day 1, 4 Hours Post dose | 13 | 6 | N.C | 0.0409 (0.0605) | 0.00 |
| HDq12 +HDq16 (n=13) | Day 1, 8 Hours Post dose | 12 | 9 | 0.05 (3.78) | 0.0973 (0.102) | 0.0672 |
| HDq12 +HDq16 (n=13) | Day 2 | 12 | 12 | 0.11 (2.21) | 0.146 (0.110) | 0.0903 |
| HDq12 +HDq16 (n=13) | Day 3 | 12 | 12 | 0.11 (2.06) | 0.137 (0.0947) | 0.112 |
| HDq12 +HDq16 (n=13) | Day 5 | 11 | 11 | 0.08 (1.86) | 0.0933 (0.0481) | 0.0854 |
| HDq12 +HDq16 (n=13) | Day 8 | 13 | 13 | 0.07 (1.75) | 0.0794 (0.0413) | 0.0682 |
| HDq12 +HDq16 (n=13) | Day 15 | 13 | 12 | 0.04 (1.76) | 0.0435 (0.0199) | 0.0385 |
| HDq12 +HDq16 (n=13) | Day 22 | 11 | 9 | 0.02 (1.76) | 0.0213 (0.0148) | 0.0232 |
| HDq12 +HDq16 (n=13) | Day 29 | 12 | 5 | N.C | 0.00766 (0.00958) | 0.00 |

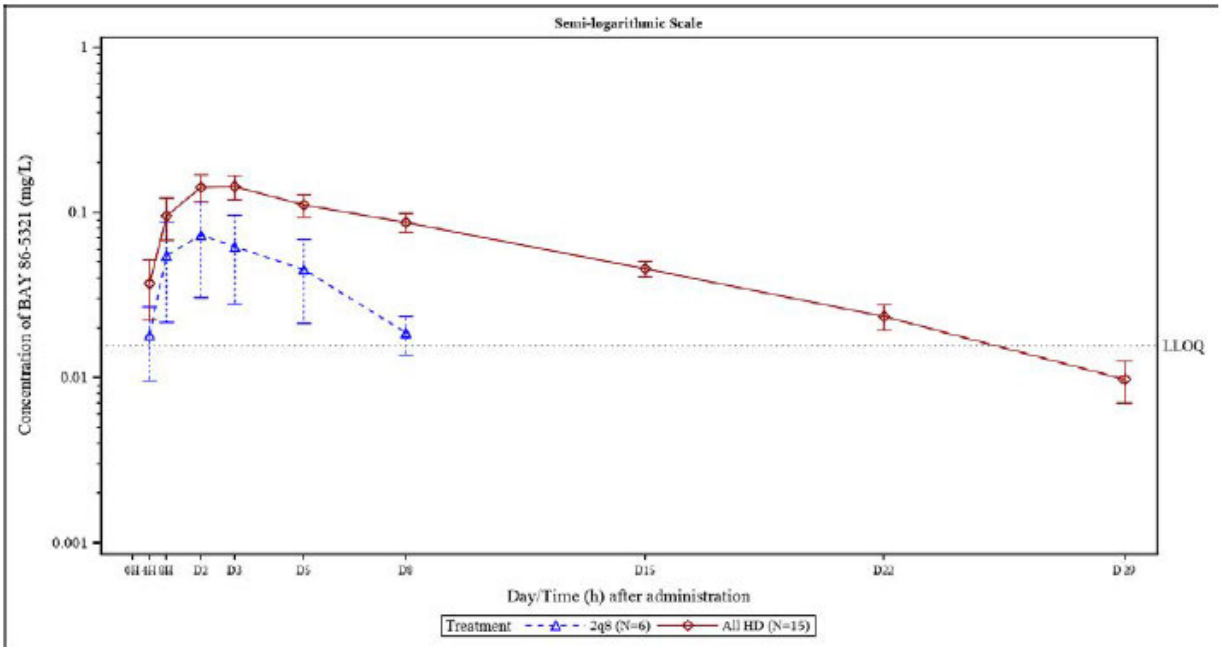
Arithm. = arithmetic, DPKS = dense pharmacokinetic analysis set, LLOQ = Lower level of quantification, geom. = geometric, N = Number of participants with unilateral treatment up to Week 48, n = Number of observations, nAMD = neovascular (wet) age- related macular degeneration, PK = pharmacokinetic, SD = 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. Minimum and Maximum have been rounded to 4 decimal places. See Definition of terms for treatment group description.
Source: Table 14.4/2.1 (post-hoc)

From the Clinical Pharmacology Review:
The clinical pharmacokinetics of HD aflibercept is summarized as below:

a. 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.
b. 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.
c. 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 Cmax and median Tmax 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.
d. 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.

e. Based on population PK covariates analysis, no dose adjustment is recommended by body weight, age, albumin, disease population, and race.
f. 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).
g. 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.



## 10. Advisory Committee Meeting

An Advisory Committee Meeting was not held to discuss this application. The application raised no new issues that were believed to benefit from an external discussion.

## 11. Labeling

The Physician's Package Insert that follows is based on a submission by Regeneron with modifications proposed by this reviewer and final revisions on June 23, 2023, by Regeneron as requested by the Agency. The Agency had no objection to the revised package insert.

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

## 12. Regulatory Action

Review of this application, as amended, has been completed. The Review Team has determined that this application can be approved in its present form. Adequate and well controlled clinical trials support the safety and efficacy of Eylea HD in the treatment of the proposed indications (Neovascular Age Related Macular Degeneration (nAMD), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR)). The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product were found to comply with the current good manufacturing practice regulations in parts 210 and 211. The proposed proprietary name, Eylea HD was found acceptable during the current review cycle. The proposed package insert, carton and container labeling is consistent with the labeling regulations.

An approval action letter will be issued.

| | |
|---|---|
| Rhea Lloyd, MD | Clinical Team Leader, Division of Ophthalmology |
| William M. Boyd, MD | Deputy Division Director, Division of Ophthalmology. |
| Wiley A. Chambers, MD | Division Director, Division of Ophthalmology |

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**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.**

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/s/

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RHEA A LLOYD
08/18/2023 05:23:37 PM

WILEY A CHAMBERS
08/18/2023 05:26:19 PM

# Clinical, Team Leader, and Division Director Review of BLA 761355

| | |
|---|---|
| **Application Type** | Original BLA |
| **Application Number** | BLA 761355 (IND 12462) |
| **Priority or Standard** | Priority (based on use of Priority Review Voucher for Medical Counter Measures) |
| **Submit Date** | December 27, 2022 |
| **Received Date** | December 27, 2022 |
| **PDUFA Goal Date** | June 27, 2023 |
| **Division/Office** | Division of Ophthalmology/Office of Specialty Medicine |
| **Review Completion Date** | June 27, 2023 |
| **Established/Proper Name** | Aflibercept |
| **(Proposed) Trade Name** | Eylea HD |
| **Applicant** | Regeneron Pharmaceuticals, Inc. |
| **Dosage Form** | Intravitreal Injection |
| **Product concentration** | Aflibercept 114.3 mg/mL |
| **Dosing Regimen** | 8 mg monthly intravitreal injection (delivered as 0.07mL) x 3 followed by q8-16 weeks for nAMD and DME. 8 mg monthly intravitreal injection (delivered as 0.07mL) x 3 followed by q8-12 weeks for DR. |
| **Proposed Indications** | Neovascular Age Related Macular Degeneration (nAMD), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) |
| **Recommendation on Regulatory Action** | Complete Response |

## Glossary

| | |
|---|---|
| AC | advisory committee |
| AE | adverse event |
| AMD | age-related macular degeneration |
| AR | adverse reaction |
| BLA | biologics license application |
| BPCA | Best Pharmaceuticals for Children Act |
| BRF | Benefit Risk Framework |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| CRF | case report form |
| CRO | contract research organization |
| CSR | clinical study report |
| DMC | data monitoring committee |

| | |
|---|---|
| DME | diabetic macular edema |
| DR | diabetic retinopathy |
| eCTD | electronic common technical document |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GCP | good clinical practice |
| ICH | International Council for Harmonization |
| IND | Investigational New Drug Application |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| nAMD | neovascular age-related macular degeneration |
| NDA | new drug application |
| NME | new molecular entity |
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PD | pharmacodynamics |
| PI | prescribing information or package insert |
| PK | pharmacokinetics |
| PMC | post-marketing commitment |
| PMR | post-marketing requirement |
| PP | per protocol |
| PPI | patient package insert |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGE | special government employee |
| SOC | standard of care |
| TEAE | treatment emergent adverse event |

# 1. Executive Summary

## 1.1. Product Introduction

Aflibercept is an inhibitor of vascular endothelial growth factor (VEGF). It is a recombinant fusion protein consisting of extracellular domains 2 and 3 of human VEGF receptors, VEGFR-1 and VEGFR-2, fused to the Fc portion of human immunoglobulin VEGF is overexpressed in several retinal diseases with neovascularization.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

In three adequate and well controlled trials, 8 mg of aflibercept administered intravitreally every 8 to 16 weeks was non-inferior to 2 mg administered every 8 weeks for the treatment of nAMD and DME. Eight (8) mg of aflibercept administered intravitreally every 8-12 weeks was non-inferior to 2 mg aflibercept administered every 8 weeks for the treatment of DR.

## 1.3. Benefit-Risk Integrated Assessment

The benefits of aflibercept 8 mg administered intravitreally outweigh the risk because studies PHOTON (VGFTe-HD-DME-1934), CANDELA (VGFTe[HD]-AMD-1905 and PULSAR (20968), demonstrated the non-inferiority (margin of 4 letters) of aflibercept 8 mg dosed every 8-12 weeks to aflibercept 2 mg dosed every 8 weeks in the treatment of nAMD, DME and DR. Studies CANDELA (VGFTe[HD]-AMD-1905 and PULSAR (20968), demonstrated the non-inferiority (margin of 4 letters) of aflibercept 8 mg dosed every 16 weeks to aflibercept 2 mg dosed every 8 weeks in the treatment of nAMD, and DME. The most common ocular adverse events after treatment with aflibercept 8 mg included cataract, conjunctival hemorrhage, intraocular pressure increased, ocular discomfort/eye pain/eye irritation, vision blurred, vitreous floaters, vitreous detachment, corneal epithelium defect, and retinal hemorrhage. Serious adverse events were reported rarely. There is clinical safety and efficacy to support the approval of the application.

However, the Review Team has determined that we cannot approve this application in its present form. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product do not comply with the current good manufacturing practice regulations in parts 210 and 211. FDA conveyed deficiencies to the representative of the drug product manufacturing facility listed in this application following a pre-license inspection of the (b) (4) facility. Satisfactory resolution of the observations will be required before this BLA submission may be approved.

Benefit-Risk Dimensions

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Vision loss in nAMD results from the abnormal growth and leakage of blood vessels in the macula.<br>• DR is a microangiopathy that occurs in both Type 1 and Type 2 DM. The pathology includes upregulation of vascular endothelial growth factor (VEGF) and other angiogenic, inflammatory and vascular permeability factors.<br>• The most common cause of vision loss from DR is DME, which can occur at any stage of DR and is characterized by retinal edema and retinal thickening. | IVT-administered anti-VEGF therapies, like aflibercept, inhibit neovascular vessel growth and leakage in the retina, and they are currently the standard of care for patients with nAMD, and serve as an alternative treatment in DME and DR when blood sugar control failures. |
| Current Treatment Options | • Lucentis, Eylea, Vabysmo and Beovu are approved for the treatment of AMD and DME. Lucentis, and Eylea are approved for the treatment of DR. Multiple corticosteroids are approved for the treatment of DME. Avastin is prescribed off-label for the treatment of AMD, DME and DR. | Approval of an alternative dosing regimen will provide options for treating individuals with nAMD, DME and DR. |
| Benefit | • Treatment of AMD, DME and DM can prevent vision loss. | 8 mg of aflibercept administered intravitreally every 8 to 16 weeks was non-inferior to 2 mg administered every 8 weeks for the treatment of nAMD and DME. Eight (8) mg of aflibercept administered intravitreally every 8-12 weeks was non inferior to 2 mg aflibercept administered every 8 weeks for the treatment of DR. |
| Risk and Risk Management | • The most common ocular adverse events after treatment with aflibercept 8 mg were cataract, conjunctival hemorrhage, intraocular pressure increased, ocular discomfort/eye pain/eye irritation, vision blurred, vitreous floaters, vitreous detachment, corneal epithelium defect, and retinal hemorrhage. Serious adverse events were reported rarely. | Routine post market monitoring and reporting of all adverse events can potentially identify rare adverse reactions not observed in clinical trials. |

## 2. Patient Experience Data Relevant to this Application (check all that apply)

| | | | | |
|---|---|---|---|---|
| ☒ | The patient experience data that was submitted as part of the application include: | | | Section where discussed, if applicable |
| | ☒ | Clinical outcome assessment (COA) data, such as | | |
| | | ☐ | Patient reported outcome (PRO) | |
| | | ☒ | Observer reported outcome (ObsRO) | Section 6 AMD and DME |
| | | ☒ | Clinician reported outcome (ClinRO) | Section 6 DR |
| | | ☐ | Performance outcome (PerfO) | |
| | ☐ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | |
| | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | ☐ | Observational survey studies designed to capture patient experience data | | |
| | ☐ | Natural history studies | | |
| | ☐ | Patient preference studies (e.g., submitted studies or scientific publications) | | |
| | ☐ | Other: (Please specify) | | |
| ☐ | Patient experience data that were not submitted in the application, but were considered in this review: | | | |
| | | ☐ | Input informed from participation in meetings with patient stakeholders | |
| | | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | |
| | | ☐ | Observational survey studies designed to capture patient experience data | |
| | | ☐ | Other: (Please specify) | |
| ☐ | Patient experience data was not submitted as part of this application. | | | |

# 3. Therapeutic Context

## 3.1. Analysis of Condition

Vision loss in nAMD results from the abnormal growth and leakage of blood vessels in the macula. DR is a microangiopathy that occurs in both Type 1 and Type 2 DM. The pathology of DR includes upregulation of vascular endothelial growth factor (VEGF) and other angiogenic, inflammatory and vascular permeability factors. The most common cause of vision loss from DR is DME, which can occur at any stage of DR and is characterized by retinal edema and retinal thickening.

## 3.2. Analysis of Current Treatment Options

Lucentis (ranibizumab injection), Eylea (aflibercept), Vabysmo (faricimab-svoa) and Beovu (brolucizumab-dbll) are approved for the treatment of AMD and DME. Lucentis and Eylea are approved for the treatment of DR. Multiple corticosteroids are approved for the treatment of DME. Avastin is prescribed off-label for the treatment of AMD, DME and DR. Regulatory Background

## 3.3. U.S. Regulatory Actions and Marketing History

Aflibercept 2 mg is an approved product in the US for the following indications:

| | |
|---|---|
| Original BLA 125387: Treatment of neovascular (wet) AMD | 11/18/2011 |
| S004: Treatment of macular edema secondary to CRVO | 9/21/2012 |
| S037: Treatment of diabetic macular edema DME | 7/29/2014 |
| S043: Treatment of macular edema secondary to BRVO | 10/6/2014 |
| S048: Treatment of diabetic retinopathy in patients with DME | 3/25/2015 |
| S061: Treatment of diabetic retinopathy | 5/13/2019 |
| S075: Treatment of retinopathy of prematurity | 2/8/2023 |

## 3.4. Summary of Pre-submission/Submission Regulatory Activity

- The Agency confirmed that for a "rearrangement of dose" (a higher amount of drug with less frequent dosing), a single non-inferiority adequate and well controlled study for nAMD (PULSAR) and a single non-inferiority adequate and well controlled study for DME (PHOTON) investigating extended dosing intervals (e.g., Q12W or Q16W) for HD aflibercept compared to the approved EYLEA 2mg regimen (Q8W) could serve as acceptable clinical support for registration of these indications. [FDA Meeting Minutes Reference ID: 4387341.
- At a Type C meeting on 29 November 2021, Agency agreed that it is acceptable to submit a new, original BLA to register HD aflibercept in the indications of DME and nAMD (Reference ID 4901050).
- A Type B, Pre-BLA meeting (Reference ID: 5047962) was held with FDA on 26 September 2022 wherein the Agency:
  - Reconfirmed that the submission of an original BLA was acceptable. The Agency also agreed that the cross-referencing strategy proposed by the Sponsor to EYLEA BLA (125387) is acceptable.
  - Indicated that the PHOTON and PULSAR study designs and statistical analysis plans (SAPs), as proposed and conducted, are sufficient for filing a new BLA for nAMD and DME indications.
  - Confirmed that the PHOTON study results are sufficient for review of a submission filing for a broad DR indication, with the FDA requiring that the Sponsor consider a 10% non-inferiority margin for the endpoint of proportion of patients with a ≥2 step improvement in Diabetic Retinopathy Severity Scale (DRSS) Score.
  - The Agency confirmed that the draft Table of Contents provided in Regeneron's meeting briefing package appears reasonable. Additionally, the Agency agreed that since PHOTON and PULSAR are single studies for separate indications, the requirement for a pooled analyses for integrated efficacy and safety is waived.
  - The Agency confirmed that a 'vial-only' presentation would be regulated solely as a biological product, whereas the 'vial kit' presentation (consisting of syringe, filter needle and injection needle) is a convenience kit that will be regulated as a combination product.

## 3.5. Foreign Regulatory Actions and Marketing History

Eylea 2 mg is marketed for a variety of indications throughout the world. Eylea HD 8 mg is not approved in any jurisdiction.

# 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

## 4.1. Office of Scientific Investigations (OSI)

From the Clinical Inspection Summary: The clinical sites of Drs. Ernest, Win, and Sarrafizadeh were inspected in support of this BLA. Based on the results of these inspections, Protocols 1934 and 20968 appears to have been conducted adequately and the data generated by these sites appear acceptable in support of the proposed indication.

## 4.2. Product Quality

This marketing application provides support for regulatory review and approval of HD (8 mg) aflibercept, a novel drug product able to deliver a higher milligram dose of aflibercept (8 mg; delivered as a 0.07 mL intravitreal [IVT] injection of 114.3 mg/mL) for the treatment of adult patients with nAMD, diabetic macular edema (DME), and diabetic retinopathy (DR). The drug product includes two presentations, a 'vial-only' presentation consisting of a vial (primary container in a carton) and a 'vial kit' - a convenience kit consisting of a vial co-packaged in a carton with a syringe (510(k) cleared (b) (4), filter needle (Class I exempt device) and injection needle (510(k) cleared, (b) (4)).

**Proposed Formulation for Eylea HD**

| Component | Function | Quality Standard | Concentration | Content per Vial (mg)[a] | Content per 0.07 mL Withdrawable Volume (mg) |
|---|---|---|---|---|---|
| Aflibercept | Active ingredient | Regeneron specification | 114.3 mg/mL | (b) (4) | 8.00 |
| (b) (4) arginine (b) (4) hydrochloride | (b) (4) | USP, Ph. Eur., JP | (b) (4) | | 0.737 |
| (b) (4) histidine | | USP, Ph. Eur., JP | | | 0.040 |
| L-histidine (b) (4) hydrochloride monohydrate | | Ph. Eur., JP | | | 0.093 |
| Sucrose | | NF, Ph. Eur., JP | (b) (4) % (w/v) | | 3.50 |
| Polysorbate 20 | | NF, Ph. Eur., JPE | (b) (4) % (w/v) | | 0.021 |
| Water for Injection | | USP, Ph. Eur., JP | QS | | QS |

(mg)[a] Calculations are based on a target fill volume of (b) (4) mL/vial. JP, Japanese Pharmacopeia; JPE, Japanese Pharmaceutical Excipients; NF, National Formulary; Ph. Eur., European; USP, United States Pharmacopeia; w/v, weight by volume.

## Comparison between Eylea HD and Eylea

| Ingredient | Function | Eylea Drug Product Concentration (mg/mL) | Eylea HD Drug Product Concentration (mg/mL) |
|---|---|---|---|
| Aflibercept | Active Ingredient | 40 | 114.3 |
| (b) (4) arginine (b) (4) hydrochloride | (b) (4) | | (b) (4) |
| (b) (4) histidine | | | |
| L-histidine (b) (4) hydrochloride monohydrate | | | |
| Sodium phosphate, monobasic, monohydrate | | (b) (4) | |
| Sodium phosphate, dibasic, heptahydrate | | | |
| Sodium chloride | | | |
| Sucrose | | | (b) (4) |
| Polysorbate 20 | | | |
| Water for Injection (WFI) | | Quantity sufficient | |

(b) (4)

USP=United States Pharmacopeia, BP=British Pharmacopeia, Ph. Eur.=European Pharmacopeia, JP=Japanese Pharmacopeia, JPE=Japanese Pharmaceutical Excipients, NF=National Formulary.

## Specifications for Drug Product

| Test | Method | Acceptance Criteria | |
|---|---|---|---|
| | | Release | End of Shelf-Life |
| Physical form/condition | Visual inspection USP <790><br>Ph. Eur. *2.9.20* JP *<6.06>* | Liquid essentially free from visible particulates | Same as release |
| Clarity | Comparison to reference suspension USP <855><br>Ph. Eur. *2.2.1* JP *<2.61>* | Not more turbid than reference suspension IV | Same as release |
| Color | Comparison to reference solutions USP <1061><br>Ph. Eur. *2.2.2* JP*<2.65>* | Not more colored than reference solution BY4 | Same as release |
| pH | Potentiometry USP <791><br>Ph. Eur. *2.2.3* JP *<2.54>* | (b) (4) | Same as release |
| Identity by Dot Blot | Dot blot | Conforms to standard | Not tested |
| Total protein content ($A_{280}$) | UV spectrophotometry | (b) (4) mg/mL | Same as release |
| Potency | Cell based bioassay | (b) (4) % of reference standard | Same as release |
| Purity by reduced CE- SDS<br>% Purity<br>% R1<br>% LMW Less R1 | Capillary electrophoresis- sodium dodecyl sulfate | (b) (4) | |
| Purity by non-reduced CE-SDS | | | |
| Purity by SE-UPLC<br>% Purity<br>% Aggregate | Liquid chromatography | | |

| Test | Method | Acceptance Criteria | |
|---|---|---|---|
| | | Release | End of Shelf-Life |
| Charge variant analysis by iCIEF<br><br>% Region 1<br>% Region 2<br>% Region 3 | Isoelectric focusing | The test article electropherogram should be qualitatively similar to the reference standard electropherogram in terms of intensity, number and pattern of peaks.<br>(b) (4) % | Same as release |
| (b) (4) content | (b) (4) HPLC/UV | (b) (4) | |
| Endotoxin content | KTA USP <85><br>Ph. Eur. *2.6.14* JP *<4.01>* | (b) (4) EU/mL | Not tested |
| Sterility (filled container) | Membrane filtration USP <71><br>Ph. Eur. *2.6.1* JP *<4.06>* | Meets USP, Ph. Eur., and JP requirements | Not tested |
| Particulate matter content<br>Particles ≥ 10µm<br>Particles ≥ 25µm<br>Particles ≥ 50µm | Light Obscuration<br>USP <788> and <789><br>Ph. Eur. *2.9.19*<br>JP *<6.07>* | ≤ (b) (4) particles/mL<br>≤ particles/mL<br>≤ particles/mL | Same as release |
| Volume in container | Volume in container USP <697><br>Ph. Eur. *2.9.17*<br>JP *<6.05>* | 0.07 mL minimum withdrawable content | Not tested |
| Container Closure Integrity (CCI) | Mass extraction USP <1270> | Not tested | No leak detected |

$A_{280}$, absorbance at 280 nm; EU, endotoxin units; HMW, high molecular weight; HPLC, high performance liquid chromatography; iCIEF, imaged capillary isoelectric focusing; JP, Japanese Pharmacopeia; KTA, kinetic turbidimetric assay; LMW, low molecular weight; CE-SDS, capillary electrophoresis-sodium dodecyl sulfate; SE-UPLC, size-exclusion ultra-performance liquid chromatography; UV, ultraviolet

**Reviewer's Comments:** *Acceptable.*

**Summary of Quality Assessments- Office of Biotechnology Products**

Aflibercept (Eylea high dose [HD]) is manufactured from (b) (4), for the same presentations (single-dose vial and single-dose vial kit) and route of administration (intravitreal injection) for which Eylea is currently approved. The Eylea HD product is a sterile aqueous buffered solution, pH 5.8, containing 114.3 mg/mL aflibercept, (b) (4)-arginine (b) (4) hydrochloride, (b) (4) histidine, (b) (4)% (w/v) sucrose, and (b) (4)% (w/v) polysorbate 20. The DP is filled into a (b) (4) glass vial with an (b) (4) stopper, and sealed with an aluminum seal cap. Each vial has a 0.07 mL withdrawable volume providing a dose of 8 mg, which allows for extended dosing intervals (up to 16 weeks).

The potency of aflibercept is evaluated though a bioassay that measures the ability of aflibercept to bind recombinant human VEGF121 (rhVEGF121) ligand and inhibit the effect of VEGF receptor activity in a transfected (b) (4) clonal cell line. The transfected (b) (4) cells express two chimeric receptors incorporating the VEGFR1 extracellular domain fused to the cytoplasmic domain of either IL18Rα or IL18Rβ, and an integrated NFκB luciferase-IRES-eGFP reporter gene.

Upon rhVEGF121 binding, the extracellular VEGFR1 dimerizes and the IL18Rα or IL18Rβ intracellular domains interact and can signal through the NFκB driven luciferase reporter gene. Potency results are reported as percentage relative to a qualified reference material. The drug substance (DS) manufacturing process consists of (b) (4)

The overall manufacturing control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for Eylea HD (aflibercept) as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. The BLA is recommended for approval from a product quality perspective.

However, while adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for the DS manufacturing facility, Regeneron Pharmaceuticals, Inc., (IOPS Rensselaer; Rensselaer, NY; FEI: 1000514603; pre-license inspection waived due to recent inspection history), the pre-license inspections at the DP manufacturing site, (b) (4) identified a 3-item form FDA-483, Inspectional Observations and the firm did not provide adequate responses to address these observations. A withhold decision is recommended for (b) (4) facility and satisfactory resolution of the observations is required before this facility can be approved.

**List of Deficiencies to be Communicated**- N/A

**List of Post-Marketing Commitments/Requirements**
"Post-marketing commitment to perform real-world shipping studies (b) (4) (b) (4) (b) (4). Since a decision on the approvability of the DP manufacturing facility was not reached before sign-off of this memo, refer to the action letter for whether this study was sent as a PMC or an additional comment in the case of a Complete Response."

**Assessment of Common Technical Document- Quality Module 1**

Environmental Assessment of Claim of Categorical Exclusion
In Section 1.12.14, Regeneron requested categorical exclusion from the environmental assessment requirement under 21 CFR 25.15(d) and 21 CFR 25.31. These claims of categorical exclusions are acceptable for BLA 761355.

**Primary Container Labeling Assessment**
The OBP review of drug product labeling was performed by Liming Lu.

**Manufacturing Summary**
Facility Assessment Recommendation: **Withhold**

A Pre-License Inspection at the proposed Drug Product manufacturing facility, (b) (4) was conducted from (b) (4), with a 3-item form FDA-483 issued. The 483 observations, firm's written FDA-483 response (dated (b) (4)) and RAI responses (dated (b) (4)) were reviewed. In summary, the firm's responses and corrective actions to the FDA Form 483 observations are deemed inadequate because: (b) (4)

(b) (4)

The proposed (b) (4) facility, Regeneron Pharmaceuticals, Inc. (FEI 1000514603), and the DS/DP testing facility, (b) (4) are acceptable based on their currently acceptable cGMP compliance status and recent relevant inspectional coverage.

(b) (4) are acceptable based on the previous acceptable inspectional history.

The proposed alternative (b) (4) manufacturer, (b) (4) ), was withdrawn from the current application on 6/5/2023.

## 4.3. Nonclinical Pharmacology/Toxicology

The nonclinical development program was designed to evaluate the in vivo pharmacology and toxicology profiles of high dose aflibercept formulation. One new in vivo pharmacology study in rabbits and 2 new repeat-dose IVT toxicity studies in monkeys with monthly administration for 3 months (total of 4 injections) and 6 months (total of 7 injections) were conducted.

The pharmacology study conducted in a chronic retinal neovascularization (RNV) model in rabbits support the hypothesis that increasing the IVT dose of aflibercept in humans will result in a longer durability of effect. Eyes that received a single IVT dose of 2 mg/eye (corresponding to a human dose of approximately 8 mg/eye based on a vitreous volume of 1.17 mL in rabbits and 4.0 mL in humans) remained complete leak-free for a longer period compared to eyes that received 500 µg/eye (corresponding to a human dose of approximately 2 mg/eye).

The 3-month IVT toxicity study evaluated the marketing formulation at a concentration of 140 mg/mL (enriched with high molecular weight species). The 6-month IVT toxicity study evaluated several aflibercept formulations at concentrations of 80 or 140 mg/mL, with Formulation 2 having a similar composition as the marketing formulation except for a higher concentration of histamine (b) (4)

mM in the marketing formulation). The formulation concentrations were 2 to 3.5X higher than the approved 40 mg/mL for EYLEA®.

The nonclinical safety profile of the high dose aflibercept formulations were generally comparable to the previously established safety profile of EYLEA®. Across studies with the aflibercept high dose formulations, there were no adverse ocular effects at any dose level. Ocular findings were limited to generally mild, transient ocular inflammation (low scores of aqueous cell or flare [0.5 to 1+] and/or vitreous cell [0.5 to 1+]) consistent with findings previously reported with the EYLEA formulation in the same species. The ocular NOAEL was the high dose 7 mg/eye. When normalized for vitreal volume (2 mL in monkeys and 4 mL in humans), the ocular NOAEL is 1.8-fold higher than the intended human dose of 8 mg.

In the 6-month ocular toxicity study, the only extraocular findings observed were microscopic changes in the respiratory epithelium of the nasal turbinates. The findings included erosion and/or ulceration (minimal to marked), squamous metaplasia (minimal to moderate), and hemorrhage (minimal to slight). The findings were observed at both doses evaluated, 4 and 7 mg/eye. There was no NOAEL. Most findings were reversible or showed partial reversibility during the 12-week recovery period.

The nasal turbinate findings were noted at doses ≥ 2 mg/eye of EYLEA®, with a NOAEL of 0.5 mg/eye. These findings are acknowledged in the EYLEA® label. The Applicant is using the same language as that accepted for EYLEA® with corrected exposure margin. At the NOAEL of 0.5 mg/eye in monkeys, the systemic exposure (AUC) for free aflibercept was approximately 3 times higher than the population pharmacokinetic estimated exposure observed in humans after an IVT dose of 8 mg. In the PULSAR, CANDELA, and PHOTON studies, an analysis of treatment emergent adverse events of nasomucosal findings was conducted with no indication of a safety signal in the 8 mg aflibercept groups compared to 2 mg. Dr. Rivera's Review recommended approval from a Pharmacology/Toxicology perspective.

## 4.4. Devices

| Packaging Component | Vial | Stopper |
|---|---|---|
| Description | (b) (4) glass, (b) (4) colorless, sterile | 13 mm, (b) (4), gray, (b) (4) (b) (4) sterile |
| Supplier Name | (b) (4) | (b) (4) |
| DMF Reference Number | DMF (b) (4) | DMF (b) (4)<br>DMF<br>DMF |

DMF, drug master file

### Vial and Stopper Release Testing Requirements

| Aspect | Method |
|---|---|
| Incoming QC Inspection[a] | In-house procedure |
| Dimensional Inspection[a] | |
| Visual Inspection[a] | |
| Quality | Vial: USP <660>, Ph. Eur. *3.2.1,* and JP *<7.01>*<br>Stopper: USP <381>, Ph. Eur. 3.2.9, JP <7.03> |
| Sterility | USP <71> |
| Endotoxin | USP <85> |

[a] Test is performed as part of reduced testing.

EU, endotoxin unit; JP, Japanese Pharmacopeia; Ph. Eur, European Pharmacopeia; QC, Quality Control; USP, United States Pharmacopeia

(b) (4), (b) (5)

[redacted]

An Intercenter Consult Memorandum was obtained from the Office of Health Technology 3, Center for Devices and Radiologic Health (CDRH). The Summary is included below.

| | |
|---|---|
| **Device Presentation(s)** | Co-packaged syringe |
| Objective of this Memo: | Provide recommendation on the use of the co-packaged device constituent with the drug product, intended for intravitreal injection under review. |
| Review **Comments**: | The proposed device constituent is a 1 mL graduated syringe manufactured by (b) (4) [redacted] under 510(k) (b) (4) [redacted] This syringe is commonly selected by drug product manufacturers as the co-packed delivery device to be used with drug products intended for various ocular injections. In prior consulting reviews for the device constituent, we have cited gaps in the evaluation of biocompatibility given the 510(k) clearance of the syringe predates several revisions to the ISO 10993 series and corresponding Biocompatibility FDA Guidance. Consistent with our prior reviews, we recommend that the sponsor work with the syringe manufacturer, (b) (4) [redacted] to evaluate the additional biocompatibility endpoint for ocular irritation. More specifically, we recommend that the sponsor evaluate intravitreal injection irritation, with a method similar to that used for ocular irritation testing per ISO 10993-23, with an additional criterion for the evaluation of white blood cell counts in the vitreous fluid from each eye. In prior reviews with this recommendation, subsequent internal discussion within the CDER review division resulted in a determination of minimal risk associated with ocular irritation and therefore no additional biocompatibility evaluation was requested of the sponsor. Therefore, we are deferring the lead CDER division for an evaluation of the biocompatibility benefit/risk profile to determine whether additional biocompatibility evaluation is needed and thus we are unable to make an approvability/disapprovability recommendation. |
| **Recommendation**: | Approvability Recommendation is deferred to CDER. |

### 4.6 Pediatric Waiver Request

The applicant has requested a waiver of pediatric assessments for AMD because pediatric studies are impossible or highly impracticable as AMD does not occur in the pediatric population. *The Division of Ophthalmology concurred with this waiver request.*

## 5. Sources of Clinical Data

**Listing of Clinical Studies for the Aflibercept Clinical Development Program**

| Study Number Report Location | Study Population | Study Design Treatment Duration | Study Objectives | Treatment, Dose, and Regimen |
|---|---|---|---|---|
| VGFTe (HD)-AMD-1905 (CANDELA) Study 21086<br><br>Module 5.3.5.1<br><br>Completed (completion date: 30 Nov 2021) through Week 44 | Men or women ≥50 years of age with active subfoveal CNV secondary to nAMD | Phase 2, multicenter, randomized, single-masked, active-controlled<br><br>Treatment duration 44 weeks | **Primary:**<br>To determine the safety of HD aflibercept<br><br>To determine if HD aflibercept provides greater intraocular pharmacodynamic effect and/or longer duration of action compared to aflibercept 2 mg | Aflibercept IVT: 2 mg IAI: aflibercept 2 mg administered monthly as 3 initial injections (baseline, Weeks 4 and 8), followed by additional doses at Weeks 20 and 32[a] HD: aflibercept 8 mg administered monthly for 3 initial injections (baseline, Weeks 4 and 8), followed by additional doses at Weeks 20 and 32 |
| Study 20968 (PULSAR)<br>Module 5.3.5.1<br><br>Last participant last visit for the Week 48 primary endpoint: 27 Jul 2022 DBL: 24 Aug 2022<br><br>Ongoing (Week 48 completed) | Men or women ≥50 years of age with active subfoveal CNV secondary to nAMD | Phase 3, multicenter, randomized (1:1:1), double-masked, active-controlled<br><br>Treatment duration 96 weeks[b] | **Primary:**<br>To determine if treatment with HD aflibercept at intervals of 12 or 16 weeks provides non-inferior BCVA change compared to aflibercept 2 mg every 8 weeks in participants with nAMD<br><br>**Secondary:**<br>To determine the effect of HD versus aflibercept 2 mg on other visual and anatomic measures of response<br><br>To assess the efficacy of 8 mg compared to aflibercept 2 mg on vision-related quality of life<br><br>To evaluate the safety of aflibercept<br><br>To evaluate the PK and immunogenicity of aflibercept | Aflibercept IVT: 2q8: aflibercept 2 mg administered every 8 weeks after 3 initial monthly injections<br><br>HDq12: aflibercept 8 mg administered every 12 weeks after 3 initial monthly injections<br><br>HDq16: aflibercept 8 mg administered every 16 weeks after 3 initial monthly injections |
| VGFTe-HD-DME-1934 (PHOTON) Study 21091<br>Module 5.3.5.1 | Men or women ≥18 years of age with | Phase 2/3, multicenter, randomized (1:2:1), | **Primary:**<br>To determine if treatment with HD aflibercept at intervals of 12 or 16 weeks provides | Aflibercept IVT:<br>2q8: aflibercept 2 mg administered every 8 weeks |

| | | | | |
|---|---|---|---|---|
| Last participant last visit for the Week 48 primary endpoint: 30 May 2022<br>DBL: 19 Aug 2022<br><br>Ongoing (Week 48 completed) | type 1 or type 2 diabetes mellitus | double-masked, active-controlled<br><br>Treatment duration 96 weeks[b] | on-inferior BCVA change compared to aflibercept 2 mg dosed every 8 weeks<br><br>**Secondary:**<br>To determine the effect of HD versus aflibercept 2 mg on anatomic and other visual measures of response<br>To evaluate the safety, immunogenicity, and PK of aflibercept | after 5 initial monthly injections<br><br>HDq12: aflibercept 8 mg administered every 12 weeks after 3 initial monthly injections<br><br>HDq16: aflibercept 8 mg administered every 16 weeks after 3 initial monthly injections |

2q8=aflibercept 2 mg administered every 8 weeks; BCVA=best corrected visual acuity; DCO=data cut-off; HDq12=aflibercept 8 mg administered every 12 weeks; HDq16=aflibercept 8 mg administered every 16 weeks; IAI=intravitreal aflibercept injection; CNV=choroidal neovascularization; CSR=clinical study report; DME=diabetic macular edema; HD=high dose; IVT=intravitreal; nAMD=neovascular age-related macular degeneration; PK=pharmacokinetics; SAF=safety analysis set.

[a] Additional treatment could be given at Weeks 24, 28, 36, and 40 if participants met pre-specified criteria as defined in Module 5.3.5.1, CANDELA CSR.

[b] Studies are planned to be extended beyond Week 96 by approximately 1 year (60 weeks).

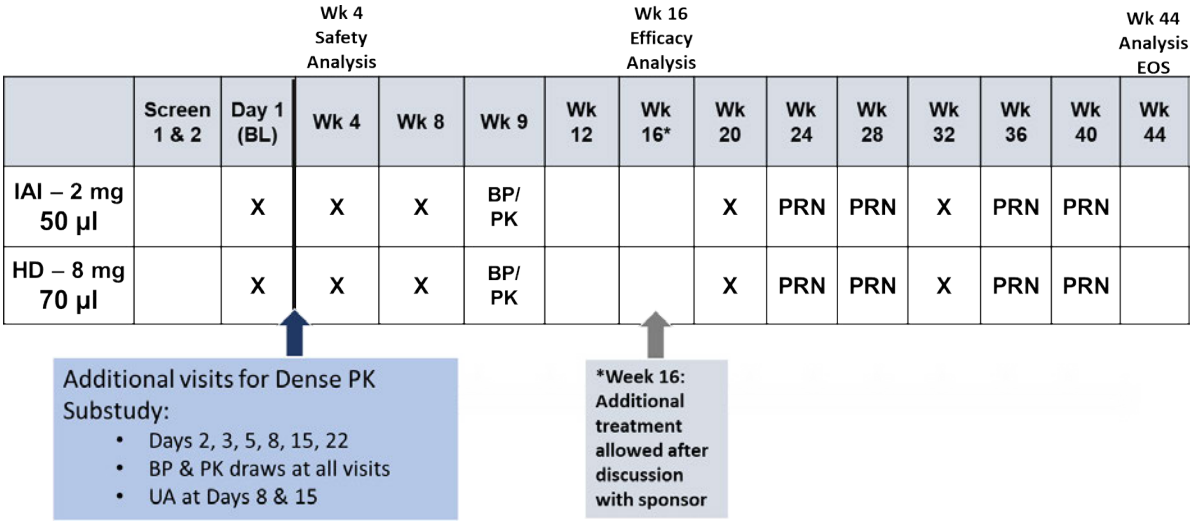
## 6. Review of Relevant Individual Trials Used to Support Efficacy

**Study 1: 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

**Trial Design**: Phase 2, multi-center, randomized, single-masked, 44-week study in participants with nAMD, 8 mg versus 2 mg. Participants were seen monthly through week 44. A total of approximately 100 eligible participants were randomized into 2 groups in a 1:1 ratio. Within each treatment group, 15 participants (total of 30) were also included in the dense PK substudy. The investigational product was administered intravitreally (IVT) monthly for 3 initial injections (baseline, week 4, and week 8), followed by additional doses at weeks 20 and 32. At week 16, additional treatment ("rescue") could be given after consultation with the Sponsor, if in the investigator's judgement, a patient could not adhere to the protocol-specified dosing interval due to persistent or worsening disease and required an interim injection. At weeks 24, 28, 36, and 40, participants were evaluated and given a dose (at their randomized dose level) if EITHER of the following criteria were met (pro re nata [PRN] criteria):

- Loss of ≥ 5 letters from week 20 Best Corrected Visual Acuity (BCVA) due to disease progression OR
- Anatomical findings that were considered vision-threatening, such as worsening or persistent retinal fluid, new or worsening retinal pigment epithelial detachment (PED), new or persistent hemorrhage, etc.




Abbreviations: BL=baseline; BP=blood pressure; EOS=end of study; HD=high-dose aflibercept (8 mg) injection; IAI=intravitreal aflibercept (2 mg) injection; PK=pharmacokinetics; PRN=pro re nata; wk=week.

**Key Inclusion Criteria**

1. ≥50 years of age with active subfoveal CNV secondary to nAMD, including juxtafoveal lesions that affect the fovea in the study eye as assessed by an independent reading center
2. Best Corrected Visual Acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 78 to 24 (Snellen equivalent of 20/32 to 20/320) in the study eye

**Key Exclusion Criteria**

- Evidence of CNV due to any cause other than nAMD in either eye
- Subretinal hemorrhage in the study eye that is ≥50% of the total lesion area
- Prior use of IVT or systemic anti-VEGF agents (aflibercept, ranibizumab, bevacizumab, brolucizumab, pegaptanib sodium) or intraocular/periocular corticosteroids in the study eye
- Prior IVT investigational agents in either eye (e.g., anti-ang-2/anti-VEGF bispecific monoclonal antibodies, gene therapy)
- History of vitreoretinal surgery (including scleral buckling) in the study eye
- Pregnant or breastfeeding women, women of childbearing potential who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 90 days after the last dose.

**Study Endpoints**

The primary efficacy endpoint was the proportion of participants without retinal fluid in the center subfield at week 16. The statistical analysis was performed using the chi-square test at the 2-sided 5% significance level. The 95% CIs were provided based on normal approximation.
For the primary analysis, missing post-baseline values for a given participant were imputed using the last observation carried forward (LOCF) procedure to determine the participant's primary efficacy response. Data from participants who received additional treatment were censored from the time additional treatment was administered at week 16. Participants were considered as non-responders if all post-baseline observations were missing.

**Reviewer's Comments:** *The primary efficacy endpoint is not considered by the Agency to be*

*predictive of clinical benefit and would not be accepted to support the efficacy of the product. For the purposes of the Agency's review, best corrected visual acuity was assessed to evaluate efficacy.*

**Exploratory Efficacy Analysis**
For the categorical exploratory endpoints, analyses were performed in the same manner as for the primary efficacy analysis. The continuous exploratory endpoints (such as mean change in CRT, mean change in BCVA, mean change in lesion size and CNV size) were summarized descriptively. They were also analyzed using an analysis of covariance model with treatment as the main effect and baseline measurement as covariate.

**Compliance with Good Clinical Practices:** Studies were conducted in compliance with good clinical practice guidelines.

**Patient Disposition by Treatment Group (All Randomized Patients)**

| | **2 mg (N=53)** | **8 mg (N=53)** |
|---|---|---|
| Number of patients who completed | 49 (92.5%) | 51 (96.2%) |
| Number of Patients who Discontinued from the Study | 4 (7.5%) | 2 (3.8%) |
| Adverse Event (Glioblastoma) | 0 | 1 (1.9%)[a] |
| Withdrawal of consent by subject | 4 (7.5%) | 1 (1.9%) |
| Study discontinuation due to COVID-19 | 1 (1.9%) | 0 |

Abbreviations: COVID-19=Coronavirus Disease 2019
[a] This event was not treatment-emergent, as it occurred after the end of the treatment-emergent study period (i.e., more than 30 days after last treatment).

**Table of Demographic Characteristics**

| | **2 mg (N=53)** | **8mg (N=53)** |
|---|---|---|
| Gender | | |
| Male | 17 (32%) | 23 (43%) |
| Female | 36 (68%) | 30 (57%) |
| Ethnicity | | |
| Hispanic or Latino | 4 (7.5%) | 2 (3.8%) |
| Not Hispanic or Latino | 49 (92.5%) | 51 (96.2%) |
| Race | | |
| White | 51 (96%) | 52 (98%) |
| American Indian or Alaska native | 1 (2%) | 0 |
| Native Hawaiian or Other Pacific islander | 0 | 1 (2%) |
| Other | 1 (2%) | 0 |
| Age (years) | | |
| Mean (SD) | 77.7 (8.3) | 77.0 (7.7) |
| Median | 78.0 | 78.0 |
| Q1 : Q3 | 73: 83 | 70: 84 |
| Min : Max | 52 : 97 | 62 : 91 |
| ≥ 50-< 65 | 4 (7.5%) | 3 (5.7%) |
| ≥ 65 | 49 (92.5%) | 50 (94.3%) |
| Baseline BCVA (letters) in study eye | | |
| Mean (SD) | 58.2 (10.5) | 57.9 (13.6) |
| Median | 59.0 | 59.0 |
| Q1 : Q3 | 52.0: 66.0 | 53.0: 69.0 |
| Min : Max | 33: 75 | 23: 78 |
| Study eye mean baseline CRT (microns) (SD) | 488.1 (204.8) | 516.2 (175.6) |
| Median | 441.0 | 459.0 |

| | | |
|---|---|---|
| Q1 : Q3 | 360.0: 527.0 | 409.0: 584.0 |
| Min : Max | 192: 1271 | 223: 1128 |
| Study eye mean baseline CNV area ($mm^2$) (SD) | 7.9 (6.2) | 7.5 (6.9) |
| Median | 6.3 | 5.3 |
| Q1 : Q3 | 4.6: 9.3 | 2.9: 9.7 |
| Min : Max | 1 : 39 | 0 : 34 |

## Efficacy

### Proportion of Participants Without Fluid in the Center Subfield of the Study Eye, LOCF at Week 16 and Week 44 (Full Analysis Set)

| Treatment | Participants without Fluid | Difference (%) (95% CI) | p-value |
|---|---|---|---|
| Week 16 | | | |
| 8mg | 27/53 (51%) | 17% (-1.6, 35.5) | 0.077 |
| 2mg | 18/53 (34%) | | |
| Week 44 | | | |
| 8mg | 21/53 (40%) | 11% (-6.6, 29.2) | 0.2185 |
| 2mg | 15/53 (28%) | | |

Abbreviations: CI=confidence interval; IRF=intraretinal fluid; LOCF=last observation carried forward; SRF=subretinal fluid. No fluid=absence of IRF and/SRF in the center subfield. Center subfield=the circular area in 1 mm diameter centered around the center point of the fovea.

### Proportion Analysis of Patients Able to Maintain a 12 - Week Dosing Interval from Week 8 through Week 44 (Full Analysis Set)

| | 2 mg (N=53) | 8 mg (N=53) |
|---|---|---|
| All Full Analysis Patients | 53 | 53 |
| Patients that received at least one dose, n (%) | 53 (100%) | 53 (100%) |
| Patients dosed per-protocol*, n (%) | 24 (45.3%) | 29 (54.7%) |
| Patients not dosed at week 16, n (%) | 40 (75.5%) | 43 (81.1%) |
| Patients not dosed at any of week 16, 24 and 28, n (%) | 30 (56.6%) | 34 (64.2%) |
| Patients not dosed at any of week 16, 24, 28 and 36, n (%) | 28 (52.8%) | 33 (62.3%) |
| Patients not dosed at any of week 16, 24, 28, 36 and 40, n (%) | 26 (49.1%) | 30 (56.6%) |
| Patients with opportunity to reach week 16 [1], n (%) | 51/53 (96.2%) | 53/53 (100%) |
| Patients that had week 16 visit, n (%) | 48/53 (90.6%) | 53/53 (100%) |
| Patients not dosed at week 16, n (%) | 35/48 (72.9%) | 43/53 (81.1%) |
| Patients dosed at week 16, n (%) | 13/48 (27.1%) | 10/53 (18.9%) |
| Patients that had week 20 visit, n (%) | 51/53 (96.2%) | 53/53 (100%) |
| Patients not dosed at week 16, n (%) | 28/51 (54.9%) | 34/53 (64.2%) |
| Patients that had week 32 visit, n (%) | 50/53 (94.3%) | 51/53 (96.2%) |
| Patients not dosed at any of week 16 24 and 28**, n (%) | 28/50 (56.0%) | 33/51 (64.7%) |
| Patients that had week 36 visit, n (%) | 49/53 (92.5%) | 50/53 (94.3%) |
| Patients not dosed at any of week 16 24 and 28**, n (%) | 28/49 (57.1%) | 33/50 (66.0%) |
| Patients that had week 40 visit, n (%) | 49/53 (92.5%) | 51/53 (96.2%) |
| Patients not dosed at any of week 16, 24, 28 and 36**, n (%) | 25/49 (51.0%) | 32/51 (62.7%) |
| Patients that had week 44 visit, n (%) | 49/53 (92.5%) | 51/53 (96.2%) |
| Patients not dosed at any of week 16, 24, 28, 36 and 40**, n (%) | 24/49 (49.0%) | 29/51 (56.9%) |

**Mean Change from Baseline in BCVA Score (ETDRS Letters) in Study Eye – Line Plot by Visit, LOCF (Full Analysis Set)**

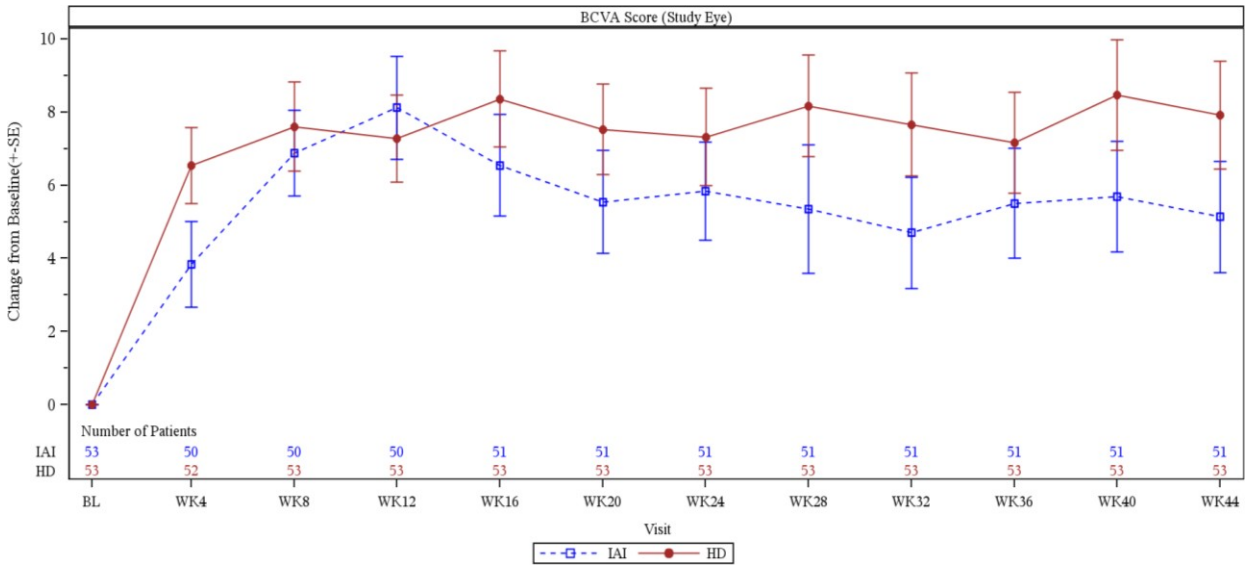
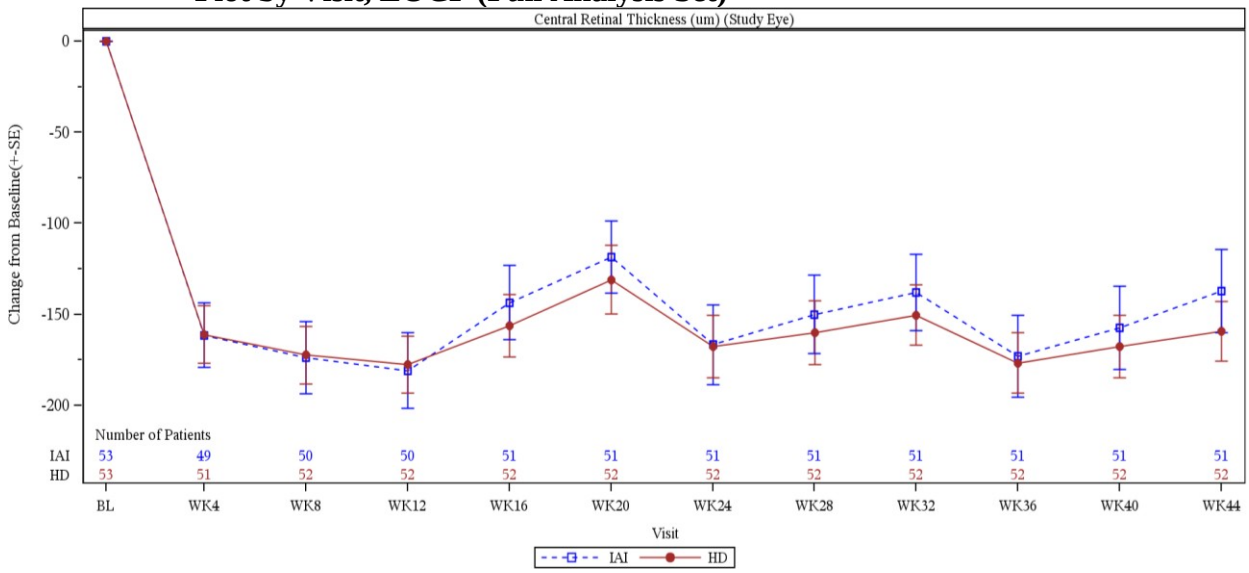



**Table 14.02.06/1.a ANCOVA of Change from Baseline in BCVA Score (ETDRS Letters) in Study Eye by Visit, LOCF (Full Analysis Set)**

| Visit | Treatment Group | Num. of Patients | Baseline (SD) | Means (SD) | Mean Change (SD) | p-value | Difference and 95% CI (LS mean) |
|---|---|---|---|---|---|---|---|
| Week 4 | 8 mg | 52 | 57.9 (13.7) | 64.5 (13.6) | 6.5 (7.5) | | 2.7 ( -0.4, 5.7) |
| Week 4 | 2 mg | 50 | 58.0 (10.7) | 61.9 (12.7) | 3.8 (8.3) | | |
| Week 8 | 8 mg | 53 | 57.9 (13.6) | 65.5 (13.9) | 7.6 (8.9) | | 0.7 ( -2.6, 4.0) |
| Week 8 | 2 mg | 50 | 58.0 (10.7) | 64.9 (12.6) | 6.9 (8.3) | | |
| Week 12 | 8 mg | 53 | 57.9 (13.6) | 65.2 (15.1) | 7.3 (8.7) | | -0.8 ( -4.5, 2.8) |
| Week 12 | 2 mg | 50 | 58.0 (10.7) | 66.2 (13.8) | 8.1 (9.9) | | |
| Week 16 | 8 mg | 53 | 57.9 (13.6) | 66.2 (15.0) | 8.4 (9.6) | 0.35 | 1.8 ( -2.0, 5.5) |
| Week 16 | 2 mg | 51 | 58.3 (10.7) | 64.8 (13.6) | 6.5 (9.9) | | |
| Week 20 | 8 mg | 53 | 57.9 (13.6) | 65.4 (15.2) | 7.5 (9.0) | | 1.9 ( -1.7, 5.7) |
| Week 20 | 2 mg | 51 | 58.3 (10.7) | 63.8 (14.5) | 5.5 (10.0) | | |
| Week 24 | 8 mg | 53 | 57.9 (13.6) | 65.2 (15.3) | 7.3 (9.7) | | 1.4 ( -2.3, 5.2) |
| Week 24 | 2 mg | 51 | 58.3 (10.7) | 64.1 (13.7) | 5.8 (9.6) | | |
| Week 28 | 8 mg | 53 | 57.9 (13.6) | 66.0 (16.1) | 8.2 (10.1) | | 2.8 ( -1.6, 7.2) |
| Week 28 | 2 mg | 51 | 58.3 (10.7) | 63.6 (16.3) | 5.4 (12.6) | | |
| Week 32 | 8 mg | 53 | 57.9 (13.6) | 65.5 (16.6) | 7.7 (10.2) | | 2.9 ( -1.2, 7.1) |
| Week 32 | 2 mg | 51 | 58.3 (10.7) | 63.0 (15.2) | 4.7 (10.9) | | |
| Week 36 | 8 mg | 53 | 57.9 (13.6) | 65.0 (15.7) | 7.2 (10.0) | | 1.6 ( -2.4, 5.7) |
| Week 36 | 2 mg | 51 | 58.3 (10.7) | 63.8 (14.6) | 5.5 (10.7) | | |
| Week 40 | 8 mg | 53 | 57.9 (13.6) | 66.3 (176.0) | 8.5 (11.0) | | 2.8 ( -1.5, 7.0) |
| Week 40 | 2 mg | 51 | 58.3 (10.7) | 63.9 (14.2) | 5.7 (10.8) | | |
| Week 44 | 8 mg | 53 | 57.9 (13.6) | 65.8 (16.2) | 7.9 (10.7) | 0.20 | 2.8 ( -1.4, 6.9) |
| Week 44 | 2 mg | 51 | 58.3 (10.7) | 63.4 (14.8) | 5.1 (10.8) | | |

/sasdata/Data/Production/BDM/VGFT/VGFT-HD-AMD/VGFTe-AMD-1905/Week44/Analysis_CSR/Programs/TFL/Generated/t_bcva_ancova_locf.sas (jin.li 29JUN2022 16:26 SAS Linux 9.4)

**Mean Change from Baseline in CRT (Central Subfield) in Study Eye – Line Plot by Visit, LOCF (Full Analysis Set)**




Abbreviations: CRT=central retinal thickness; HD=high-dose aflibercept (8 mg) injection; IAI=intravitreal aflibercept (2 mg) injection; LOCF=last observation carried forward; SE=standard error. LOCF=missing observations were imputed by the last non-missing post-baseline observation. For patients receiving additional treatment at week 16, measurements past week 16 were imputed using the last observation prior to additional treatment. Baseline: the latest available valid measurement taken on Study day 1prior to the administration of study drug. Source: Post-text Figure 14.02.08/5.b

**Summary of Ocular Treatment-Emergent Adverse Events of the Study Eye Reported in ≥ 2 Participants in Either Group Through Week 44 (Safety Analysis Set)**

| PT | 2 mg (n=53) | 8 mg (n=53) |
|---|---|---|
| **Number of Patients with at Least One Such AE, n (%)** | **20 (37.7%)** | **20 (37.7%)** |
| Vitreous detachment | 2 (3.8%) | 4 (7.5%) |
| Conjunctival hemorrhage | 2 (3.8%) | 3 (5.7%) |
| Dry eye | 2 (3.8%) | 2 (3.8%) |
| Neovascular age-related macular degeneration | 4 (7.5%) | 2 (3.8%) |
| Retinal tear | 0 | 2 (3.8%) |
| Punctate keratitis | 2 (3.8%) | 1 (1.9%) |
| Retinal hemorrhage | 2 (3.8%) | 1 (1.9%) |
| Visual acuity reduced | 2 (3.8%) | 1 (1.9%) |
| Visual impairment | 2 (3.8%) | 1 (1.9%) |

Abbreviations: AE=adverse event; HD=high-dose aflibercept (8 mg) injection; IAI=intravitreal aflibercept (2 mg) injection; MedDRA=medical dictionary for regulatory activities; PT=preferred term. MedDRA (Version 24.0) coding dictionary applied. TEAEs are defined as AEs occurring from the first dose of study drug to the last dose plus 30 days for participants who early discontinued, and for participants who completed the study (with week 44 visit), up to week 44 visit. The percentage is based on the number of participants in each treatment group as denominator. Source: Post-text Table 14.03.01/2-1.a

**Summary of Non-Ocular Treatment-Emergent Adverse Events in the Reported in ≥ 2 Participants in Either Group Through Week 44 (Safety Analysis Set)**

| PT | 2mg (n=53) | 8mg (n=53) |
|---|---|---|
| **Number of Patients with at Least One Such AE, n (%)** | **24 (45.3%)** | **28 (52.8%)** |
| Fall | 2 (3.8%) | 3 (5.7%) |
| Dizziness | 0 | 3 (5.7%) |
| COVID-19 | 2 (3.8%) | 2 (3.8%) |
| Diarrhea | 1 (1.9%) | 2 (3.8%) |
| Urinary tract infection | 1 (1.9%) | 2 (3.8%) |
| Nausea | 0 | 2 (3.8%) |
| Chest pain | 0 | 2 (3.8%) |
| Skin laceration | 0 | 2 (3.8%) |
| Sinusitis | 2 (3.8%) | 1 (1.9%) |
| Gastroesophageal reflux disease | 2 (3.8%) | 0 |
| Arthralgia | 2 (3.8%) | 0 |

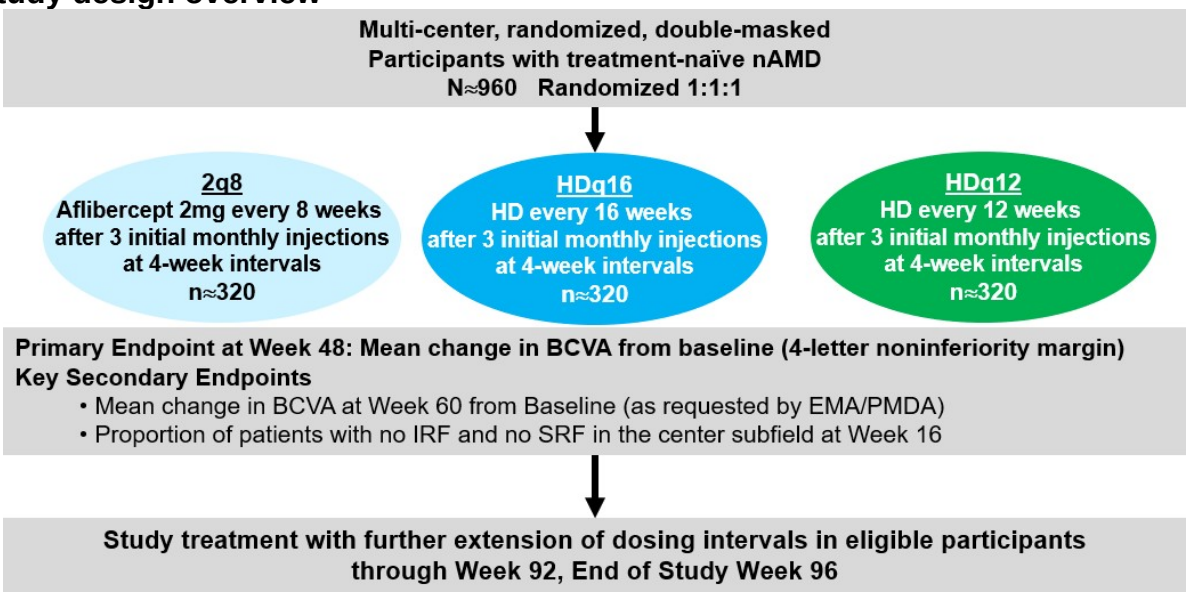
Abbreviations: AE=adverse event; HD=high-dose aflibercept (8 mg) injection; IAI=intravitreal aflibercept (2 mg) injection; MedDRA=medical dictionary for regulatory activities; PT=preferred term. MedDRA (Version 24.0) coding dictionary applied. TEAEs are defined as AEs occurring from the first dose of study drug to the last dose plus 30 days for participants who early discontinued, and for participants who completed the study (with week 44 visit), up to week 44 visit. The percentage is based on the number of participants in each treatment group as denominator. Source: Post-text Table 14.03.01/2-3.a

**Study 2:** 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

**Trial Design:** Phase 3, multi-center, randomized, double-masked, active-controlled study of IVT administration of 8 mg aflibercept versus 2 mg aflibercept in participants with **treatment-naïve nAMD**. The study continues to Week 96. Data up to Week 48 have been submitted. The study is ongoing.

## Study design overview




BCVA=best corrected visual acuity, EMA=European Medicines Agency, HD=8 mg 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.

## Dosing schedule

| | Day 1 | Wk 4 | Wk 8 | Wk 12 | Wk 16 | Wk 20 | Wk 24 | Wk 28 | Wk 32 | Wk 36 | Wk 40 | Wk 44 | Wk 48 (1° Endpoint) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2q8 | X | X | X | | X | o | X | o | X | o | X | o | X |
| HDq12 | X | X | X | | o[a] | X[a] | o | o | X[c] | o | o | X[c] | o |
| HDq16 | X | X | X | | o[b] | o[b] | X[b] | o | o | o | X[c] | o | o |

| | Wk 52 | Wk 56 | Wk 60 (Key 2° Endpoint) | Wk 64 | Wk 68 | Wk 72 | Wk 76 | Wk 80 | Wk 84 | Wk 88 | Wk 92 | Wk 96 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2q8 | o | X | o | X | o | X | o | X | o | X | o | |
| HDq12 | o | X[d] | o | o | X[d] | o | o | X[d] | o | o | X[d] | |
| HDq16 | o | X[d] | o | o | o | X[d] | o | o | o | X[d] | o | |

1º=primary, 2º=secondary, DRM=dose regimen modification, HD=high dose, IXRS=Interactive Response System, q8=every 8 weeks, q12=every 12 weeks, q16=every 16 weeks, Wk=Week, X=active injection, o=sham procedure

For masking purposes, DRM assessments were performed in all participants at all visits (through the IXRS) starting from Week 16.

a. HDq12 group: If DRM criteria were met at Week 16 or 20, participants continued on q8 rescue regimen.
b. HDq16 group: If DRM criteria were met at Week 16 or 20, participant continued on q8 rescue regimen. If DRM criteria were met at Week 24, participant continued on q12 regimen.
c. For participants remaining on a dosing interval of q12 or q16 weeks after Week 24, if DRM criteria are met at an active injection visit, the next dosing interval will be reduced by 4 weeks (to a minimum of q8).
d. From Week 52, all participants in HD groups will be eligible for dose interval shortening (to a minimum of q8) or extension (by 4-week increments) according to pre-specified DRM criteria. If DRM criteria are met at an active injection visit, the next dosing interval will be changed by 4 weeks.

This figure does not reflect all available dosing options, once a participant's dose regimen is shortened or extended.
This study started prior to the onset of the 2022 crisis between Russia and Ukraine and included study sites located in Ukraine and in Russia. All participants affected by the crisis, related findings and deviations by unique participant identifier and by investigational site, and a description of the finding or deviation were recorded.

Only one eye was treated within the study. Sham procedures were done on visits when an active injection is not planned. No sham or active procedures were done at the non-treatment visit at Week 12. At all subsequent visits, all participants are receiving either active study treatment injection or sham procedure, depending on their assigned treatment schedule and eligibility for dose regimen modification (DRM).

Starting at Week 16, participants assigned to HDq12 or HDq16 were assessed for DRM criteria at every visit:

- If a participant in the HDq12 group or the HDq16 group met DRM criteria at Week 16 or Week 20, the participant was dosed with 8 mg aflibercept at that visit and subsequently continued receiving 8 mg aflibercept every 8 weeks.
- A participant in the HDq16 group who had not met DRM criteria at Week 16 or Week 20 and met DRM criteria at Week 24 was dosed with 8 mg aflibercept at that visit and subsequently continued receiving 8 mg aflibercept every 12 weeks.
- Subsequently, participants who meet DRM criteria at any active treatment visit would have their intervals shortened by 4 weeks, to a minimum interval of 8 weeks. Starting at Week 52, all participants randomized to HDq12 or HDq16 were eligible for adjustments of their treatment intervals (shortening or extension) based on pre-specified DRM criteria, with the dose interval adjustments (shortening or extension) becoming effective at or after Week 60 (after data collection for key secondary efficacy endpoint). Participants could also be eligible for extensions of their treatment intervals according to additional DRM criteria, which are assessed in parallel with the previous shortening criteria.
- All participants were examined every 4 weeks through Week 96.

### Dose Regimen Modification (DRM)/Rescue Regimen

For masking purposes, assessments for DRM were performed in all participants at all visits (through the IXRS) starting from Week 16. Based on these assessments, participants in the HD groups could have their treatment intervals shortened or extended. The minimum interval between injections will be 8 weeks, which is considered a rescue regimen for participants randomized to HD aflibercept who are unable to tolerate a dosing interval greater than every 8 weeks. Participants in the aflibercept 2 mg group remained on fixed q8 dosing throughout the study until the end of masked study visit at Week 96 (i.e., no modifications of their treatment intervals regardless of the outcomes of the DRM assessments).

**Reviewer's Comments:** *The Agency disagreed with the unequal treatment of the participants in different treatment regimens.*

### DRM in Year 1: Baseline to Week 48

Beginning at Week 16, participants in the 8 mg groups had the dosing interval shortened (at the visits described below) if BOTH the following DRM criteria are met:

- BCVA loss >5 letters from Week 12, AND
- >25 µm increase in central retinal thickness (CRT) from Week 12 OR new foveal hemorrhage OR new foveal neovascularization

In case the Week 12 measurement was not available, the Week 8 measurement was used instead. If both, Week 12 and Week 8 measurements were not available, the Week 4 measurement was used. If a participant in the HDq12 group or the HDq16 group met both criteria at Week 16 or Week 20, the participant was dosed with 8 mg aflibercept at that visit and would continue on rescue regimen (aflibercept 8 mg, every 8 weeks). If a participant in the HDq16 group who had not met the criteria at Week 16 or Week 20 met both criteria at Week 24, the participant was dosed with 8 mg aflibercept at that visit and would continue on q12 dosing.

For participants whose interval was not shortened to q8 dosing at or before Week 24, the interval was shortened if the DRM criteria were met at subsequent visits with active injection. Participants in the HDq12 group who met the criteria would receive the planned dose at that visit and would then continue on rescue regimen (aflibercept 8 mg, every 8 weeks).

Participants in the HDq16 group who meet these criteria would receive the planned dose at that visit and will then continue to be dosed every 12 weeks if they were on a 16-week interval, or switch to the rescue regimen (aflibercept 8 mg, every 8 weeks) if they were on a 12-week interval. Therefore, a participant randomized to HDq16 whose injection interval has been shortened to q12 would have their injection interval further shortened to q8 if these criteria were met at any subsequent assessment.

### DRM Year 2: Week 52 to Week 96 (End of Masked Part of Study)

From Week 52 through the end of the masked part of study (Year 2), all participants in the HD groups would continue to have the interval shortened in 4-week intervals (to a minimum of q8) if the DRM criteria for shortening were met at visits with active injection, using the criteria described above for Year 1.

In addition to shortening of the interval, all participants in the HD groups (including HD group participants whose interval was shortened during Year 1) were eligible for interval extension (by 4-week increments) if the following DRM criteria were met at visits with active injection in Year 2:

- BCVA loss <5 letters from Week 12, AND
- No fluid at the central subfield on OCT, AND
- No new onset foveal hemorrhage or foveal neovascularization

For participants who did not meet the criteria for shortening or extension of the interval, the dosing interval was maintained. As in Year 1, all participants in all treatment groups (including the 2q8 group) were evaluated against both DRM criteria at all visits through the IXRS for masking purposes. However, changes to dosing schedule were only implemented as described above. No changes to the dosing schedule were made to the 2q8 treatment group at any time. All anatomic criteria were based on the site evaluations/OCT assessments, not on the reading center assessments.

**DRM Year 3 (Masked Transition Period and Open-label Extension Part): Week 96 to Week 156 (End of Study) / E-DRM Criteria**

The E-DRM criteria refer to new baseline (NB) which was defined as the average of values assessed at Weeks 84, 88, and 92 (with the average being rounded up to the next integer). At Week 96, no interval adjustments will be performed for any group.

Beginning at Week 100, all participants will have the dosing interval **shortened** if the following criteria are met at ANY visit (scheduled or unscheduled, with or without active injection):

1. BCVA loss >5 letters from NB BCVA due to persistent or worsening AMD, AND
2. Any of the following
   - >25 µm increase in CRT from NB CRT
   - new onset of foveal neovascularization
   - new foveal hemorrhage

   OR
3. BCVA loss >10 letters NB due to worsening AMD

If the E-DRM shortening criteria are met at any treatment, monitoring or unscheduled visit, the participant will be dosed at the same visit. If the E-DRM criteria are met at a dosing visit the subsequent interval will be shortened by 2 weeks. If the E-DRM criteria are met at a non-dosing visit, the subsequent interval will be shortened to the time from the most recent dose minus 2 weeks. Participants can be seen for unscheduled visits at any time at the investigator's discretion. Treatment intervals may not be adjusted to less than 8 weeks. Actual intervals may be slightly shorter due to the windows allowed for visits planned 8 weeks apart.

If a participant does not meet any of the E-DRM criteria but is deemed at high risk for vision loss, the participant should be brought back for evaluation within approximately 2 weeks. If E-DRM criteria are still not met, and the investigator feels there is high risk for irreversible disease progression, a dose can be given at that visit, and the subsequent interval will be shortened to the time from the most recent dose minus 2 weeks. The minimum dosing interval remains every 8 weeks (q8).

Similar to Year 2, all participants in all groups (including participants whose interval was shortened during Year 1, Year 2, or Year 3) are eligible for interval **extension** up to a maximum interval of 24 weeks, but in contrast to Year 2, intervals will now be modified by 2-week rather than 4-week increments, if all of the following E-DRM criteria are met at visits with active injection:

1. BCVA loss <5 letters from the NB, AND
2. No fluid at the central subfield on OCT, AND
3. No new onset foveal hemorrhage or foveal neovascularization

For participants who do not meet the criteria for shortening or extension of the interval, the dosing interval will be maintained. For E-DRM adjustment purposes, similar to the masked study part, all anatomic criteria will be based on the local site evaluations/OCT assessments, not on the assessments of the central reading center.

**Key Inclusion Criteria**

1. ≥18 years of age with type 1 or type 2 diabetes mellitus

2. DME with central involvement in the study eye with CRT ≥300 μm (or ≥320 μm on Spectralis) as determined by the reading center at the screening visit
3. Best Corrected Visual Acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 78 to 24 (Snellen equivalent of 20/32 to 20/320) in the study eye with decreased vision determined to be primarily the result of DME

**Key Exclusion Criteria**

1. Evidence of macular edema due to any cause other than diabetes mellitus in either eye
2. Active proliferative diabetic retinopathy in the study eye
3. Panretinal laser photocoagulation (PRP) or macular laser photocoagulation in the study eye within 12 weeks (84 days) of the screening visit
4. IVT anti-VEGF treatment (aflibercept, ranibizumab, bevacizumab, brolucizumab, pegaptanib sodium) in the study eye within 12 weeks (84 days) of the screening visit
5. Prior IVT investigational agents in either eye (e.g., anti-ang-2/anti-VEGF bispecific monoclonal antibodies, gene therapy, etc.) at any time
6. Treatment with ocriplasmin (JETREA®) in the study eye at any time
7. Previous use of intraocular or periocular corticosteroids in the study eye within 16 weeks (112 days) of the screening visit, or ILUVIEN® or OZURDEX® IVT implants at any time
8. History of vitreoretinal surgery (including scleral buckle) in the study eye
9. Any other intraocular surgery within 12 weeks (84 days) before the screening visit
10. Yttrium-aluminum-garnet (YAG) laser capsulotomy in the study eye within 4 weeks (28 days) of the screening visit
11. IOP ≥25 mmHg in the study eye
12. History of glaucoma filtration surgery in the past, or likely to need filtration surgery in the future in the study eye
13. Evidence of infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye within 4 weeks (28 days) of the screening visit
14. Any intraocular inflammation/infection in either eye within 12 weeks (84 days) of the screening visit
15. History of idiopathic or autoimmune uveitis in the study eye
16. Vitreomacular traction or epiretinal membrane in the study eye evident on biomicroscopy or OCT that is thought to affect central vision
17. Preretinal fibrosis involving the macula in the study eye
18. Any history of macular hole of stage 2 and above in the study eye
19. Current iris neovascularization, vitreous hemorrhage, or tractional retinal detachment visible at the screening assessments in the study eye
20. History of corneal transplant or corneal dystrophy in study eye
21. Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the patient beyond what is to be expected from standard procedures of IVT injections, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety
22. Only 1 functional eye, even if that eye was otherwise eligible for the study (e.g., BCVA of counting fingers or less in the eye with worse vision)
23. Structural damage to the center of the macula in the study eye that is likely to preclude improvement in BCVA following the resolution of macular edema including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia, or organized hard exudates
24. Ocular conditions with poorer prognosis in the fellow eye

25. Inability to obtain photographs, FA, or SD-OCT in the study eye, e.g., due to media opacity, allergy to fluorescein dye, or lack of venous access
26. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the patient at high risk for treatment complications
27. Any prior systemic (IV) anti-VEGF administration
28. Uncontrolled diabetes mellitus as defined by hemoglobin A1c (HbA1c) > 12%
29. Uncontrolled blood pressure (defined as systolic >160 mmHg or diastolic >95 mmHg). Patients may be treated with up to 3 agents known to have anti-hypertensive effects for arterial hypertension to achieve adequate blood pressure control. This limit applies to drugs that could be used to treat hypertension even if their primary indication in the patient was not for blood pressure control. Any recent changes in medications known to affect blood must be stable for 12 weeks (84 days) prior to screening.
30. History of cerebrovascular accident or myocardial infarction within 24 weeks (168 days) of screening visit
31. Renal failure, dialysis, or history of renal transplant
32. Known sensitivity to any of the compounds of the study formulation
33. Participation in an investigational study within 30 days prior to screening visit that involved treatment with any drug (excluding vitamins and minerals) or device
34. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the sponsor
35. Pregnant or breastfeeding women
36. Men or women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 3 months after the last dose.

Participants were randomly assigned in a 1:1:1 ratio to 1 of 3 parallel treatment groups. Randomization was stratified by geographic region (Japan vs. Rest of World), and baseline (Day 1) BCVA (< 60 vs. ≥ 60), to ensure balanced distribution of the treatment groups within each stratum.

Only 1 eye per participant could be enrolled in the study. If a participant's fellow (non-study) eye required anti-VEGF treatment during the participant's participation in the study, the fellow eye should have been treated with aflibercept 2 mg according to the approved treatment regimen in the respective country/region, irrespective of the randomization assignment of the participant. Although the fellow eye could have received treatment, it was not considered an additional study eye. Participants who received treatment for the fellow eye remained in the study.

**Disposition in overall study: Week 48 (all enrolled participants)**

| Number of subjects | 2q8 | HDq12 | HDq16 |
|---|---|---|---|
| Enrolled, n | | | |
| Randomized, n (%) | 337 (100%) | 336 (100%) | 338 (100%) |
| Treated, n (%) | 336 (99.7%) | 335 (99.7%) | 338 (100%) |
| Completed study until week 48, n (%) | 309 (91.7%) | 316 (94.0%) | 312 (92.3%) |
| Unknown if completed study until week 48 [a], n (%) | 3 (0.9%) | 2 (0.6%) | 1 (0.3%) |
| Did not complete study until week 48, n (%) | 25 (7.4%) | 18 (5.4%) | 25 (7.4%) |
| Primary reason | | | |
| Adverse event | 5 (1.5%) | 1 (0.3%) | 5 (1.5%) |
| Physician decision | 1 (0.3%) | 3 (0.9%) | 2 (0.6%) |

| | | | |
|---|---|---|---|
| Protocol deviation | 0 | 1 (0.3%) | 1 (0.3%) |
| Lost to follow-up | 1 (0.3%) | 1 (0.3%) | 0 |
| Lack of efficacy | 2 (0.6%) | 0 | 0 |
| Withdrawal by subject | 5 (1.5%) | 5 (1.5%) | 12 (3.6%) |
| Death | 5 (1.5%) | 3 (0.9%) | 1 (0.3%) |
| Other | 4 (1.2%) | 2 (0.6%) | 2 (0.6%) |
| COVID-19 pandemic | 2 (0.6%) | 2 (0.6%) | 2 (0.6%) |
| Subject decision: COVID-19 pandemic related | 2 (0.6%) | 2 (0.6%) | 2 (0.6%) |

[a]6 participants who had missing Week 48 information (i.e., they neither discontinued during Week 48 time frame, nor had Week 48 visit performed or marked as not done) were summarized as Unknown if completed study until Week 48 (see Database errata in Section 16.4.2).

**Demographics and disease characteristics (full analysis set)**

| | **2q8** | **8mg q12** | **8 mg q16** |
|---|---|---|---|
| | N = 336 | N = 335 | N = 338 |
| Gender, n (%) | | | |
| Female | 188 (56.0%) | 182 (54.3%) | 180 (53.3%) |
| Male | 148 (44.0%) | 153 (45.7%) | 158 (46.7%) |
| Race, n (%) | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 83 (24.7%) | 74 (22.1%) | 77 (22.8%) |
| Asian Indian | 0 | 0 | 0 |
| Chinese | 40 (11.9%) | 31 (9.3%) | 31 (9.2%) |
| Japanese | 34 (10.1%) | 31 (9.3%) | 33 (9.8%) |
| Korean | 9 (2.7%) | 11 (3.3%) | 12 (3.6%) |
| Thai | 0 | 0 | 0 |
| Other | 0 | 1 (0.3%) | 1 (0.3%) |
| Black or African American | 2 (0.6%) | 2 (0.6%) | 0 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| White | 249 (74.1%) | 256 (76.4%) | 260 (76.9%) |
| Not reported | 2 (0.6%) | 2 (0.6%) | 1 (0.3%) |
| Multiple | 0 | 1 (0.3%) | 0 |
| Hispanic or Latino | 12 (3.6%) | 7 (2.1%) | 9 (2.7%) |
| Not Hispanic or Latino | 322 (95.8%) | 322 (96.1%) | 326 (96.4%) |
| Not reported | 2 (0.6%) | 6 (1.8%) | 3 (0.9%) |
| Age (years) n | | | |
| Mean (SD) | 74.2 (8.8) | 74.7 (7.9) | 74.5 (8.5) |
| Median | 74.0 | 75.0 | 75.0 |
| Min, Max | 50,96 | 52,93 | 53,95 |
| Age group (years) , n (%) < 65 | 45 (13.4%) | 26 (7.8%) | 43 (12.7%) |
| ≥ 65 to < 75 | 126 (37.5%) | 137 (40.9%) | 124 (36.7%) |
| ≥ 75 to < 80 | 69 (20.5%) | 77 (23.0%) | 66 (19.5%) |
| ≥ 80 to < 85 | 59 (17.6%) | 59 (17.6%) | 66 (19.5%) |
| ≥ 85 | 37 (11.0%) | 36 (10.7%) | 39 (11.5%) |
| Mean BCVA (ETDRS letter score) (SD) | 58.9 (14.0) | 59.9 (13.4) | 60.0 (12.4) |
| Median BCVA (ETDRS letter score) | 62.0 | 62.0 | 61.0 |
| BCVA: Min, Max | 24,78 | 24,78 | 24,78 |
| Categorized BCVA (ETDRS letters score), n (%) | | | |
| ≤ 73 | 287 (85.4%) | 293 (87.5%) | 290 (85.8%) |
| > 73 | 49 (14.6%) | 42 (12.5%) | 48 (14.2%) |
| Categorized BCVA (ETDRS letters score), n (%) [a] | | | |
| < 60 | 136 (40.5%) | 141 (42.1%) | 144 (42.6%) |
| ≥ 60 | 200 (59.5%) | 194 (57.9%) | 194 (57.4%) |
| Intraocular Pressure (mmHg) Mean (SD) | 14.8 (3.0) | 14.9 (3.2) | 14.9 (3.2) |
| Intraocular Pressure (mmHg) Median | 15.0 | 15.0 | 15.0 |
| Intraocular Pressure Min, Max | 6,25 | 7,25 | 7,25 |

| | | | |
|---|---|---|---|
| Geographic atrophy (as per reading center), n (%) | | | |
| No | 328 (97.6%) | 326 (97.3%) | 326 (96.4%) |
| Yes | 3 (0.9%) | 3 (0.9%) | 6 (1.8%) |
| Not available | 5 (1.5%) | 6 (1.8%) | 6 (1.8%) |
| Polypoidal choroidal vascularization (as per reading center), n (%) | | | |
| No | 53 (15.8%) | 54 (16.1%) | 46 (13.6%) |
| Yes | 54 (16.1%) | 45 (13.4%) | 42 (12.4%) |
| Not available | 1 (0.3%) | 2 (0.6%) | 0 |
| Missing | 228 (67.9%) | 234 (69.9%) | 250 (74.0%) |
| Central subfield retinal thickness (µm, as per reading center) | | | |
| Mean (SD) | 367.1 (133.6) | 370.3 (123.7) | 370.7 (132.7) |
| Median | 343.0 | 348.0 | 340.0 |
| Min, Max | 142,1116 | 151,840 | 144,913 |
| Choroidal neovascularization size (mm², as per reading center) | | | |
| Mean (SD) | 6.359 (5.039) | 5.977 (4.831) | 6.546 (5.532) |
| Median | 4.997 | 4.899 | 4.698 |
| Min, Max | 0.148,24.129 | 0.115,30.023 | 0.000, 28.650 |
| Total lesion area (mm², as per reading center) | | | |
| Mean (SD) | 6.86 (5.41) | 6.38 (5.07) | 6.88 (5.65) |
| Median | 5.41 | 5.03 | 5.07 |
| Min, Max | 0.148,27.41 | 0.185,30.02 | 0.180,28.65 |
| Choroidal neovascularization type (as per reading center), n (%) | | | |
| Type 1 - occult or PCV | 194 (57.7%) | 198 (59.1%) | 191 (56.5%) |
| Type 2 - classic CNV | 66 (19.6%) | 68 (20.3%) | 61 (18.0%) |
| Type 1 and Type 2 – both classic and occult are present | 66 (19.6%) | 59 (17.6%) | 74 (21.9%) |
| Type 3 – RAP | 5 (1.5%) | 4 (1.2%) | 5 (1.5%) |
| Cannot grade | 0 | 0 | 1 (0.3%) |
| Not applicable - no CNV present | 5 (1.5%) | 6 (1.8%) | 6 (1.8%) |

**Summary of Treatment Exposure in Study Eye through Week 48 (Pulsar Safety Analysis Set)**

| | **2q8** (N=336) | **HDq12** (N=325) | **HDq16** (N=338) |
|---|---|---|---|
| Total number of active injections | 2267 | 1986 | 1703 |
| Total number of sham injections | 1212 | 1515 | 1793 |
| 1 active injection per patient, n (%) | 1 (0.3%) | 2 (0.6%) | 2 (0.6%) |
| 2 active injections per patient, n (%) | 1 (0.3%) | 2 (0.6%) | 1 (0.3%) |
| 3 active injections per patient, n (%) | 4 (1.2%) | 3 (0.9%) | 9 (2.7%) |
| 4 active injections per patient, n (%) | 6 (1.8%) | 7 (2.1%) | 22 (6.5%) |
| 5 active injections per patient, n (%) | 6 (1.8%) | 22 (6.6%) | 263 (77.8%) |
| 6 active injections per patient, n (%) | 29 (8.6%) | 260 (77.6%) | 11 (3.3%) |
| 7 active injections per patient, n (%) | 288 (85.7%) | 39 (11.6%) | 29 (8.6%) |
| 8 active injections per patient, n (%) | 1 (0.3%) | 0 | 0 |
| Mean number of injections (SD) | 6.7 (0.8) | 5.9 (0.8) | 5.1 (0.8) |
| Median number of injections | 7.0 | 6.0 | 5.0 |
| Min: Max | 1: 8 | 1: 7 | 1: 7 |

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; 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; The percentage was based on the number of patients in each treatment group as a denominator. Study drugs given at week 48 or beyond were not included in this table. Patients in the HD groups could have had their interval shortened if protocol specified criteria were met.

## Efficacy

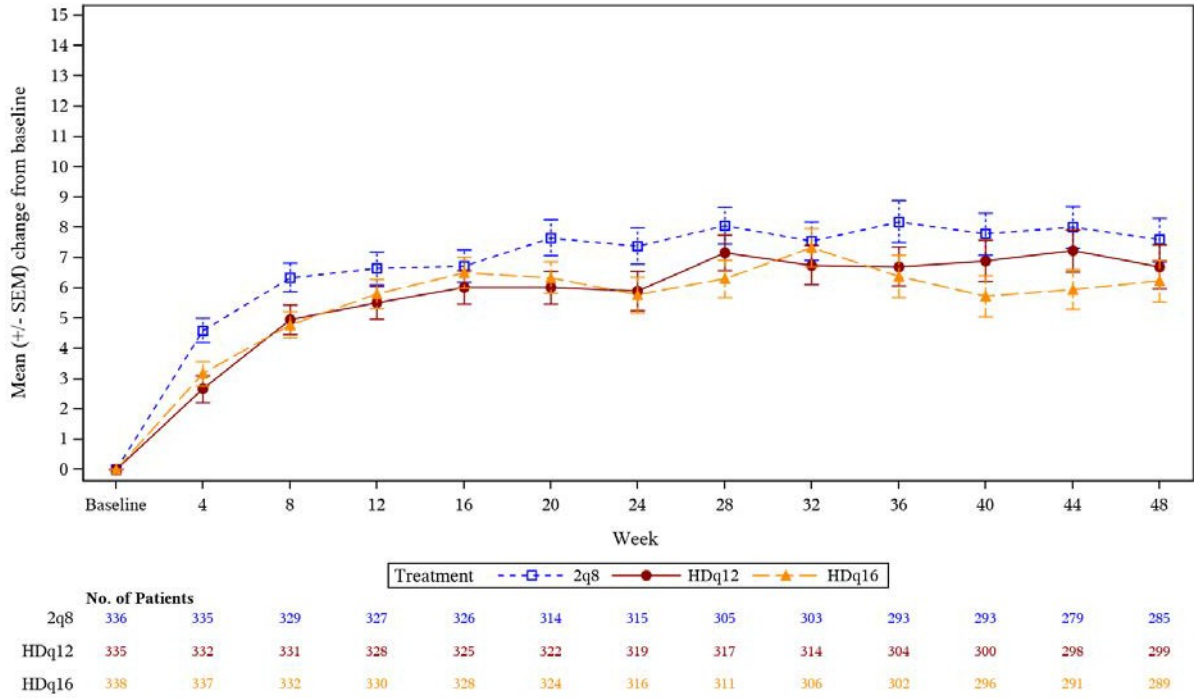
### Change from baseline in BCVA measured by the ETDRS letter score at Week 48, MMRM (full analysis set)

| | 2mg q8<br>N = 336 | 8mg q12<br>N = 335 | 8mg q16<br>N = 338 |
|---|---|---|---|
| Baseline mean[a] | 58.9 | 59.9 | 60.0 |
| Number of subjects with Week 48 data | 285 | 299 | 289 |
| Arithmetic mean (SD) change from baseline[a] | 7.6 (12.2) | 6.7 (12.6) | 6.2 (11.7) |
| LS mean (SE) change from baseline | 7.0 (0.7) | 6.1 (0.8) | 5.9 (0.7) |
| Degrees of freedom | | 622.1 | 647.7 |
| Comparison[b] | | HDq12 - 2q8 | HDq16 - 2q8 |
| t-value | | 3.14 | 3.07 |
| p-value of one-sided test for non-inferiority at a margin of 4 letters | | 0.0009 | 0.0011 |
| Estimate for Contrast and two-sided 95% CI[c] | | -1.0 (-2.9,0.9) | -1.1 (-3.0,0.7) |

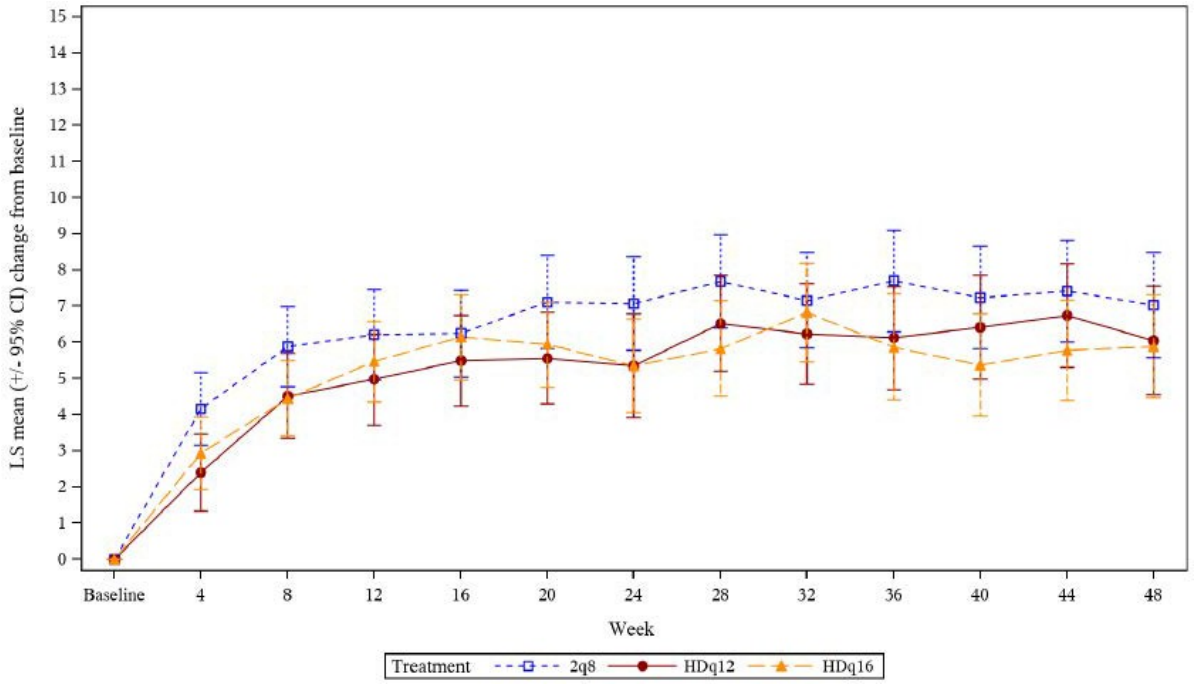
BCVA = best corrected visual acuity, CI = Confidence interval, LS = Least Square, SD = Standard deviation, SE = Standard error. A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [< 60 vs. ≥ 60]) as fixed factors, and terms for the interaction between baseline BCVA and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: unstructured. Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints as described in Table 9-12 in Section 9.5 of the SAP.
[a]Based on observed assessments.
[b]The contrast also includes the interaction term for treatment x visit (at Week 48, for details on the population-level summary see SAP Section 6.2.2.1).
[c]Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively, with two-sided 95% CIs.
See Definition of terms for treatment group description. Source: Table 14.2.1/1

**Reviewer's Comments:** *Multiple sensitivity analyses were consistent with these findings.*

**Mean change from baseline in BCVA measured by the ETDRS letter score, Observed Cases (full analysis set)**




**LSmean change from baseline in BCVA measured by the ETDRS letter score, MMRM (full analysis set)**




BCVA = best corrected visual acuity, ETDRS = Early Treatment of Diabetic Retinopathy Study, SEM= standard error mean OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded as described in the SAP. LS = least squares, SEM= standard error of the LS mean. Source: Figures 14.2.1/1 and 14.2.1/1.1

## Secondary Endpoints:

**Proportion of participants with no IRF and no SRF in central subfield at Week 16, LOCF (full analysis set)**

| | **2mg q8** N = 336 | **8mg q12** N = 335 | **8mg q16** N = 338 |
|---|---|---|---|
| Subjects who had no IRF and no SRF | 173/335 (51.6%) | 205/333 (61.6%) | 217/334 (65.0%) |
| Difference[a] % (two- sided 95% CI) | | 11.7% (5.3, 18.2) | |
| CMH test[b] p-value | | 0.0002 | |

BCVA=best corrected visual acuity, CI=confidence interval, CMH=Cochran-Mantel-Haenszel, ICE=intercurrent events, IRF=intraretinal fluid, LOCF=last observation carried forward, Num/Den=numerator/denominator, SAP=statistical analysis plan, SRF=subretinal fluid. LOCF method for the last available observed value prior to ICE was carried forward to impute missing data.
Intercurrent events (ICE) were handled according to primary estimand strategy for binary endpoints as described in Table 9-13 in Section 9.5 of the SAP.
[a]Difference is both 8 mg groups minus 2q8 and CI was calculated using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (< 60 vs. ≥ 60) and is displayed with two-sided 95% CIs.
[b]p-value for the one-sided Cochran-Mantel-Haenszel (CMH) test for superiority. Source: Table 14.2.2/1

**Reviewer's Comments:** *The Agency does not agree that "no IRF/SRF" represents a clinically significant benefit in visual function or is necessarily predictive of a visual function benefit.*

**Test decisions and statistical conclusions as per the G-SAP (full analysis set)**

| Null hypothesis | p-value (one-sided test) | Estimate for Difference (two-sided 95% CI | Test decision $H_{x0}$ rejected |
|---|---|---|---|
| **Primary endpoint "Change from baseline in BCVA at Week 48": Non-inferiority** | | | |
| H10: non-inferiority of HDq12 vs. 2q8 in primary endpoint | p = 0.0009 | -0.97 (-2.87,0.92) letters [a] | Yes |
| H30: non-inferiority of HDq16 vs. 2q8 in primary endpoint | p = 0.0011 | -1.14 (-2.97,0.69) letters [a] | Yes |
| **Key secondary endpoint "Proportion of participants with no IRF and no SRF in central subfield at Week 16": Superiority** | | | |
| $H_{50}$: superiority of pooled high dose vs. 2q8 in key secondary endpoint | p = 0.0002 | 11.733% (5.263%, 18.204%) b | Yes |
| **Primary endpoint "Change from baseline in BCVA at Week 48": Superiority** | | | |
| $H_{60}$: superiority of HDq12 vs. 2q8 in primary endpoint | p = 0.8437 | -0.97 (-2.87,0.92) letters [a] | No, and hierarchical testing procedure stopped |
| $H_{80}$: superiority of HDq16 vs. 2q8 in primary endpoint | p = 0.8884 | -1.14 (-2.97,0.69) letters a | NA (test not performed because of failure above) |

BCVA=best corrected visual acuity, CI=Confidence limits, G-SAP=Global statistical analysis plan, IRF=Intraretinal fluid, MMRM=mixed model for repeated measurements, NA=not applicable, SRF=Subretinal fluid

[a]Estimate for contrast based on the MMRM model, computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively, with two-sided 95% CIs.

[b]Difference is HD groups minus 2q8 and CI was calculated using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (< 60 vs. ≥ 60) and is displayed with two-sided 95% Cis. Sources: Table 14.2.1/1 and Table 14.2.2/1

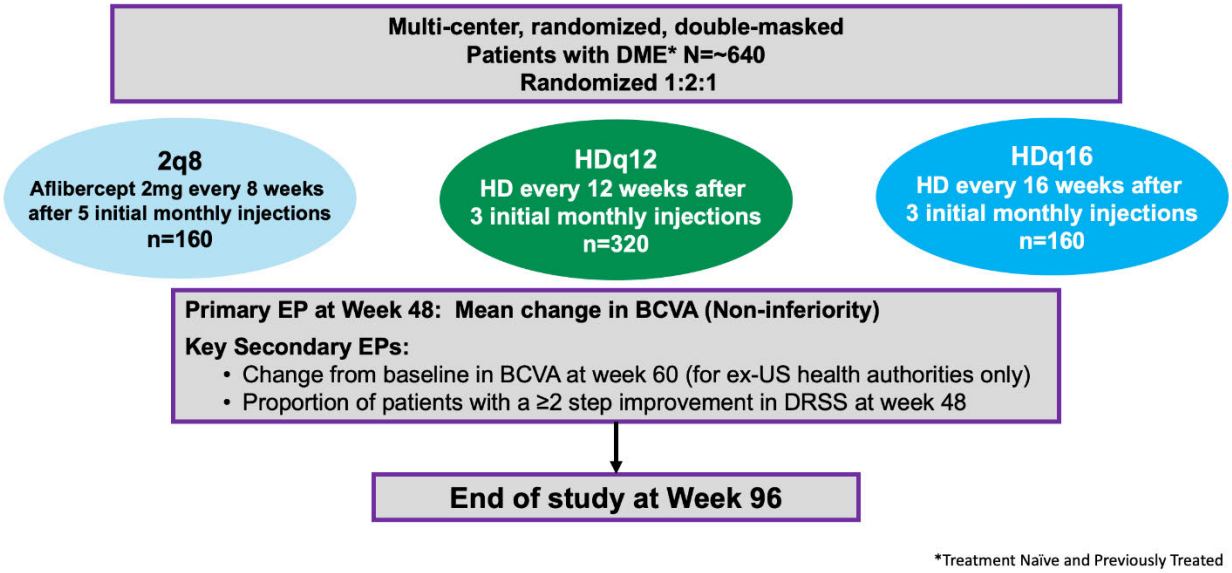
**Reviewer's Comments:** *No additional statistical testing beyond this point.*

**Study 3: Photon VGFTe-HD-DME-1934**

**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

**Trial Design:** Phase 3, multi-center, randomized, double-masked, active-controlled study of IVT administration of 8 mg aflibercept versus 2mg aflibercept in participants with Diabetic Macular Edema (DME). The study continues to Week 96. Data up to Week 48 have been submitted. The study is still ongoing.

**Study design overview**




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.

## PHOTON: Dosing Schedule

| | Day 1 | Wk 4 | Wk 8 | Wk 12 | Wk 16 | Wk 20 | Wk 24* (1° Endpoint) | Wk 28 | Wk 32 | Wk 36 | Wk 40 | Wk 44 | Wk 48 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2q8 | X | X | X | X | X | o | X | o | X | o | X | o | X |
| HDq12 | X | X | X | o | o^ | X^ | o | o | X[a] | o | o | X[a] | o |
| HDq16 | X | X | X | o | o* | o* | X* | o | o | o | X[a] | o | o |

X=active injection
o=sham injections

***Dose Regimen Modifications in Year 1***
^Q12 group: If criteria are met, patients will continue q8.
*HDq16 group: If criteria are met at week 16 or 20, patient will continue q8. If criteria are met at week 24, patient will continue q12.
[a]For patients on a dosing interval of q12 or q16 weeks, DRM criteria will be assessed at dosing visits and if DRM criteria are met the next dosing interval will be reduced by 4 weeks.

| | Wk 52 | Wk 56 | Wk 60 | Wk 64 | Wk 68 | Wk 72 | Wk 76 | Wk 80 | Wk 84 | Wk 88 | Wk 92 | Wk 96 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2q8 | o | X | o | X | o | X | o | X | o | X | o | |
| HDq12 | o | X[a] | o | o | X[a] | o | o | X[a] | o | o | X[a] | |
| HDq16 | o | X[a] | o | o | o | X[a] | o | o | o | X[a] | o | |

***Dose Regimen Modifications in Year 2***
[a]Patients that continue on a dosing interval >8 weeks will be assessed at their dosing visits for DRM criteria for both shortening and extension of the interval by 4 week increments

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HD=high dose; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week

**Dose Regimen Modifications (DRM)/Rescue Regimen**

For masking purposes, assessments for dose regimen modifications (DRMs) were performed in all participants at all visits (through the interactive web response system [IWRS]) beginning at week 16. Based on these assessments, participants in the HD groups might have had their treatment intervals shortened (year 1 and year 2) or extended (year 2). The minimum interval between injections was 8 weeks which was considered a rescue regimen for patients randomized to HD aflibercept and unable to tolerate a dosing interval greater than every 8 weeks. **Participants in the aflibercept 2mg group remained on fixed q8 dosing throughout the study (i.e., did not have modifications of their treatment intervals regardless of the outcomes of the DRM assessments).**

During the first year, beginning at week 16, participants in the 8 mg groups had the dosing interval shortened (at the visits described below) if BOTH of the following criteria were met:

a. > 10 letter loss in BCVA from week 12 in association with persistent or worsening DME AND

b. > 50 µm increase in CRT from week 12

If a patient in the HDq12 group or the HDq16 group met both criteria at week 16 or week 20, the patient was dosed with 8 mg aflibercept at that visit and continued on a rescue regimen (aflibercept 8 mg, every 8 weeks). If a patient in the HDq16 group who had not met the criteria at week 16 or 20 met both criteria at week 24, the patient was dosed with 8 mg aflibercept at that visit and continued on q12 week dosing.

For patients whose interval was not shortened to q8 dosing at or before week 24, the interval was shortened if the DRM criteria were met at a subsequent dosing visit. Patients in the HDq12 group who met the criteria received the planned dose at that visit and then continued on a rescue regimen (aflibercept 8 mg, every 8 weeks). Patients in the HDq16 group who met these criteria received the planned dose at that visit and were to be continued on an every 12-week regimen if they were on a 16-week interval, or switched to the rescue regimen (aflibercept 8 mg, every 8 weeks) if they were

previously shortened to a 12-week interval. Therefore, a patient randomized to HDq16 whose injection interval had been shortened to q12 had their injection interval further shortened to q8 if these criteria were met at any subsequent dosing visit.

**Method of Treatment Assignment**

Approximately 640 patients will be randomized into 3 treatment groups in a ratio of 1:2:1 to receive either 2 mg aflibercept every 8 weeks following 5 initial monthly doses (2q8), HD every 12 weeks following 3 initial monthly doses (HDq12), or HD every 16 weeks following 3 initial monthly doses (HDq16), according to a central randomization scheme provided by an interactive web response system (IWRS) to the designated, unmasked investigator or study coordinator (or unmasked qualified designee). Randomization will be stratified according to baseline CRT (<400 μm, ≥400 μm), prior treatment for DME (yes, no) and geographic region (Rest of world, Japan).

## Statistical Plan

There were differing requirements for the submission to various global regulatory authorities. Two (2) different testing strategies were be described in the statistical analysis plan (SAP): a global plan (G-SAP), and a plan that specifically addresses requirements from EMA and PMDA (EP-SAP). The G-SAP will constitute the primary analysis for the study. The EP-SAP will be used for submission to the EMA/PMDA regulatory authorities.

The 2 primary hypotheses to be tested are the non-inferiority (NI) of HDq12 vs. 2q8 (control) and HDq16 vs. 2q8 (control) with respect to the primary endpoint of change from baseline in BCVA at week 48. The non-inferiority margin is set at 4 letters for each of the primary hypotheses. The key secondary analysis was based on the estimand concept, similar to the primary analysis. The key secondary efficacy endpoint (proportion of participants with ≥ 2-step improvement in DRSS at week 48) was analyzed using the Cochran-Mantel-Haenszel method, stratified by baseline CRT, prior DME treatment, and geographical region as specified for the primary endpoint. The key secondary hypotheses for non-inferiority (with a non-inferiority margin of 15%) were tested according to the hierarchical testing hierarchy, based on the 2-sided 95% CIs were reported. Non-inferiority was assessed by comparing the lower bound of the 95% CI for the estimated treatment difference with the non-inferiority margin.

**The Testing Order of Hierarchical Testing Procedure[a] in G-SAP and EP- SAP**

| G-SAP | EP-SAP |
|---|---|
| $H_{10}$: Q12 BCVA Week 48 non-inferiority | $H_{10}$: Q12 BCVA Week 48 non-inferiority |
| | $H_{20}$: Q12 BCVA Week 60 non-inferiority |
| $H_{30}$: Q16 BCVA Week 48 non-inferiority | $H_{30}$: Q16 BCVA Week 48 non-inferiority |
| | $H_{40}$: Q16 BCVA Week 60 non-inferiority |
| $H_{50}$: Q12 DRSS Week 48 non-inferiority | $H_{50}$: Q12 DRSS Week 48 non-inferiority |
| $H_{60}$: Q16 DRSS Week 48 non-inferiority | $H_{60}$: Q16 DRSS Week 48 non-inferiority |
| $H_{70}$: Q12 BCVA Week 48 superiority | $H_{70}$: Q12 BCVA Week 48 superiority |
| | $H_{80}$: Q12 BCVA Week 60 superiority |
| $H_{90}$: Q16 BCVA Week 48 superiority | $H_{90}$: Q16 BCVA Week 48 superiority |
| | $H_{100}$: Q16 BCVA Week 60 superiority |

[a] for comparisons with 2q8 study treatment group

**Disposition of Participants**

This study was conducted at 138 centers that randomized participants in Canada, Czech Republic, Germany, Hungary, Japan, United Kingdom, and the United States. A total of 970 participants were screened; 310 of them were screen failures with failure to meet inclusion/exclusion criteria being the most frequent reason for screen failure. Overall, 660 participants were randomized.

| | **2q8** | **8mg q12** | **8 mg q16** |
|---|---|---|---|
| | **(N=167)** | **(N=329)** | **(N=164)** |
| Number of patients who completed Week 48 | 157 (94%) | 300 (91%) | 156 (95%) |
| Number of patients who discontinued prior to Week 48 | 10 (6%) | 29 (9%) | 8 (5%) |
| Reasons for discontinuation prior to Week 48 | | | |
| Noncompliance with protocol by the subject | 1 (0.6%) | 0 | 0 |
| Adverse event | 0 | 4 (1%) | 1 (0.6%) |
| Decision by the investigator/sponsor | 0 | 4 (1%) | 1 (0.6%) |
| Withdrawal of consent by subject | 4 (2%) | 7 (2%) | 2 (1%) |
| Lost to follow-up | 1 (0.6%) | 5 (2%) | 1 (0.6%) |
| Death | 4 (2%) | 9 (3%) | 3 (2%) |

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; 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;
Source: PTT 14.1.1.3.

**Demographics and Baseline Characteristics (Full Analysis Set)**

| | **2q8** (N=167) | **HDq12** (N=328) | **HDq16** (N=163) |
|---|---|---|---|
| Age (years) Mean (SD) | 63.0 (9.8) | 62.1 (11.1) | 61.9 (9.5) |
| Age (years) Median | 64.0 | 63.0 | 62.0 |
| Age Q1: Q3 | 56.0: 70.0 | 55.0: 70.0 | 55.0: 68.0 |
| Age Min: Max | 38: 90 | 24: 87 | 37: 83 |
| Age category, n (%) <55 years | 29 (17.4%) | 77 (23.5%) | 38 (23.3%) |
| Age category, n (%) ≥55 - <65 years | 63 (37.7%) | 108 (32.9%) | 54 (33.1%) |
| Age category, n (%) ≥65 - <75 years | 54 (32.3%) | 107 (32.6%) | 57 (35.0%) |
| Age category, n (%) ≥75 years | 21 (12.6%) | 36 (11.0%) | 14 (8.6%) |
| Ethnicity, n (%) Hispanic or Latino | 31 (18.6%) | 54 (16.5%) | 34 (20.9%) |
| Not Hispanic or Latino | 133 (79.6%) | 266 (81.1%) | 126 (77.3%) |
| Not Reported | 3 (1.8%) | 8 (2.4%) | 3 (1.8%) |
| Race, n (%) American Indian or Alaska Native | 0 | 2 (0.6%) | 0 |

| | | | |
|---|---|---|---|
| Race, n (%) Asian | 30 (18.0%) | 48 (14.6%) | 23 (14.1%) |
| Race, n (%) Black or African American | 18 (10.8%) | 35 (10.7%) | 9 (5.5%) |
| Race, n (%) Native Hawaiian or Other Pacific Islander | 0 | 1 (0.3%) | 0 |
| Race, n (%) White | 112 (67.1%) | 231 (70.4%) | 128 (78.5%) |
| Race, n (%) Other | 0 | 1 (0.3%) | 0 |
| Race, n (%) Not Reported | 4 (2.4%) | 6 (1.8%) | 1 (0.6%) |
| Gender, n(%) Female | 75 (44.9%) | 118 (36.0%) | 64 (39.3%) |
| Gender, n(%) Male | 92 (55.1%) | 210 (64.0%) | 99 (60.7%) |
| Geographical region, n (%) Japan | 20 (12.0%) | 37 (11.3%) | 17 (10.4%) |
| Rest of World | 147 (88.0%) | 291 (88.7%) | 146 (89.6%) |
| Duration of diabetes (years): Mean (SD) | 15.9 (10.04) | 15.1 (9.96) | 15.7 (10.67) |
| Duration of diabetes (years): Median | 15.2 | 14.0 | 14.4 |
| Duration of diabetes (years): Q1: Q3 | 8.9: 21.0 | 7.2: 21.3 | 6.3: 22.1 |
| Duration of diabetes Min: Max | 1:61 | 0:51 | 0:54 |
| Diabetes type, n (%) Type I | 11 (6.6%) | 18 (5.5%) | 9 (5.5%) |
| Diabetes type, n (%) Type II | 156 (93.4%) | 310 (94.5%) | 154 (94.5%) |
| Insulin Dependent | 84 (50.3%) | 150 (45.7%) | 85 (52.1%) |
| Non-Insulin Dependent | 73 (43.7%) | 160 (48.8%) | 68 (41.7%) |
| NEI-VFQ-25 total score at baseline Mean (SD) | 76.7 (15.9) | 76.8 (17.3) | 77.9 (15.6) |
| BCVA (ETDRS letter score) Mean (SD) | 61.5 (11.22) | 63.6 (10.10) | 61.4 (11.76) |
| BCVA (ETDRS letter score) Median | 63.0 | 65.0 | 64.0 |
| BCVA (ETDRS letter score) Q1: Q3 | 54.0: 70.0 | 57.0: 72.0 | 55.0: 71.0 |
| BCVA (ETDRS letter score) Min: Max | 24: 78 | 27: 79 | 29: 78 |
| Baseline BCVA category ≤73 letters | 147 (88.0%) | 269 (82.0%) | 140 (85.9%) |
| Baseline BCVA category >73 letters | 20 (12.0%) | 59 (18.0%) | 23 (14.1%) |
| CRT (microns) Mean (SD) | 457.2 (144.0) | 449.1 (127.4) | 460.3 (117.8) |
| CRT Median | 417.0 | 431.0 | 432.0 |
| CRT Q1 : Q3 | 346.0: 532.0 | 359.0: 518.0 | 371.0: 540.0 |
| CRT Min: Max | 260: 1014 | 229: 1309 | 255: 926 |
| CRT Missing | 0 | 1 | 0 |
| CRT category per reading center[a] <400 microns | 72 (43.1%) | 134 (40.9%) | 65 (39.9%) |
| CRT category per reading center[a] ≥400 microns | 95 (56.9%) | 194 (59.1%) | 98 (60.1%) |
| CRT category per IWRS[b] (used for stratification) <400 microns | 69 (41.3%) | 138 (42.1%) | 69 (42.3%) |
| CRT category per IWRS[b] (used for stratification) ≥400 microns | 98 (58.7%) | 190 (57.9%) | 94 (57.7%) |
| Intraocular Pressure Mean (SD) | 15.9 (2.99) | 15.3 (3.24) | 14.9 (3.25) |
| Intraocular Pressure Median | 16.0 | 15.0 | 15.0 |
| Intraocular Pressure Q1: Q3 | 14.0: 18.0 | 13.0: 18.0 | 13.0: 17.0 |
| Intraocular Pressure Min: Max | 8: 23 | 8: 24 | 7: 24 |
| Diabetic Retinopathy Severity Score (DRSS) 10 | 0 | 1 (0.3%) | 2 (1.2%) |
| Diabetic Retinopathy Severity Score (DRSS) 12 | 0 | 2 (0.6%) | 0 |
| Diabetic Retinopathy Severity Score (DRSS) 14 | 1 (0.6%) | 1 (0.3%) | 1 (0.6%) |
| Diabetic Retinopathy Severity Score (DRSS) 15 | 1 (0.6%) | 0 | 0 |
| Diabetic Retinopathy Severity Score (DRSS) 20 | 3 (1.8%) | 13 (4.0%) | 2 (1.2%) |
| Diabetic Retinopathy Severity Score (DRSS) 35 | 66 (39.5%) | 121 (36.9%) | 66 (40.5%) |
| Diabetic Retinopathy Severity Score (DRSS) 43 | 34 (20.4%) | 59 (18.0%) | 36 (22.1%) |
| Diabetic Retinopathy Severity Score (DRSS) 47 | 17 (10.2%) | 46 (14.0%) | 15 (9.2%) |
| Diabetic Retinopathy Severity Score (DRSS) 53 | 22 (13.2%) | 34 (10.4%) | 11 (6.7%) |
| Diabetic Retinopathy Severity Score (DRSS) 61 | 9 (5.4%) | 20 (6.1%) | 9 (5.5%) |
| Diabetic Retinopathy Severity Score (DRSS) 65 | 4 (2.4%) | 11 (3.4%) | 9 (5.5%) |
| Diabetic Retinopathy Severity Score (DRSS) 71 | 1 (0.6%) | 1 (0.3%) | 2 (1.2%) |
| Diabetic Retinopathy Severity Score (DRSS) 75 | 0 | 1 (0.3%) | 0 |
| Diabetic Retinopathy Severity Score (DRSS) 90 (non-gradable) | 9 (5.4%) | 18 (5.5%) | 10 (6.1%) |

Abbreviations: 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; 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; CRT=central retinal thickness; DME=Diabetic macular edema; DRSS=Diabetic Retinopathy Severity Score; EDC=electronic data capture; ETDRS=early treatment diabetic retinopathy study; HD=high dose; IWRS=interactive web response system; max=maximum; min=minimum;

n=number; Q=quartile; SD=standard deviation.
[a]Baseline values; used for subgroup analyses
[b]Reflects site's entry of reading center values from screening visit into IWRS; 10 patients were stratified incorrectly, based on incorrect data entry in IWRS.
[c]Used for subgroup analyses
[d]Reflects entry of prior DME treatment information by site into IWRS; 47 patients had data entered inconsistently between IWRS and EDC.
Source: PTT 14.1.2.3

## Summary of Treatment Exposure in Study Eye through Week 48 (Photon Safety Analysis Set)

| | **2q8** (N=167) | **HDq12** (N=328) | **HDq16** (N=163) |
|---|---|---|---|
| Total number of active injections | 1292 | 1875 | 806 |
| Total number of sham injections | 580 | 1720 | 1054 |
| 1 active injection per patient, n (%) | 2 (1.2%) | 2 (0.6%) | 1 (0.6%) |
| 2 active injections per patient, n (%) | 0 | 7 (2.1%) | 1 (0.6%) |
| 3 active injections per patient, n (%) | 0 | 11 (3.4%) | 3 (1.8%) |
| 4 active injections per patient, n (%) | 2 (1.2%) | 11 (3.4%) | 6 (3.7%) |
| 5 active injections per patient, n (%) | 2 (1.2%) | 12 (3.7%) | 146 (89.6%) |
| 6 active injections per patient, n (%) | 3 (1.8%) | 273 (83.2%) | 2 (1.2%) |
| 7 active injections per patient, n (%) | 10 (6.0%) | 12 (3.7%) | 4 (2.5%) |
| 8 active injections per patient, n (%) | 148 (88.6%) | 0 | 0 |
| Mean number of injections (SD) | 7.7 (0.98) | 5.7 (0.96) | 4.9 (0.61) |
| Median number of injections | 8.0 | 6.0 | 5.0 |
| Q1: Q3 | 8.0: 8.0 | 6.0: 6.0 | 5.0: 5.0 |
| Min: Max | 1: 8 | 1: 7 | 1: 7 |

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; 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; The percentage was based on the number of patients in each treatment group as a denominator. Study drugs given at week 48 or beyond were not included in this table. Patients in the HD groups could have had their interval shortened if protocol specified criteria were met. Source: PTT 14.1.4.1

**Summary of Treatment Exposure in the Study Eye Through Week 48**

| | 2q8 (N=157) | HDq12 (N=300) | HDq16 (N=156) |
|---|---|---|---|
| Patients maintained with q12 or longer dosing interval, n (%) | NA | 273 (91.0%) | 150 (96.2%) |
| Patients maintained with q16 dosing interval, n (%) | NA | NA | 139 (89.1%) |
| Patients with q12 or longer dosing interval as the last[a] intended dosing interval, n (%) | NA | 262 (87.3%) | 146 (93.6%) |
| Patients with q16 dosing interval as the last[a] intended dosing interval, n (%) | NA | NA | 136 (87.2%) |
| Patients shortened to q8 dosing interval at week 16, n (%) | NA | 3 (1.0%) | 1 (0.6%) |
| Patients shortened to q8 dosing interval at week 20, n (%) | NA | 12 (4.0%) | 3 (1.9%) |
| Patients with a shortened dosing interval anytime, n (%) | NA | 27 (9.0%) | 17 (10.9%) |
| Patients with a shortened dosing interval to q8 anytime, n (%) | NA | 27 (9.0%) | 6 (3.8%) |
| Patients with a shortened dosing interval to q12 anytime [b], n (%) | NA | NA | 13 (8.3%) |

Abbreviations: NA=Not applicable; 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; 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; All HD= / indicates categories that did not apply. [a] Refers to the patient's assigned interval at week 48. [b] Includes participants who were only shortened to q12 as well as participants who were shortened to q12 and further shortened to q8. Source: PTT 14.1.4.2

**Primary Endpoint -- Change from Baseline in BCVA (ETDRS Letters) at Week 48 in the Study Eye, MMRM (Full Analysis Set)**

| Treatment | LS Mean (SE) change from BL | Mean (SD) change from BL | BL Mean | Number of patients with Week 48 data | DF | Difference [a] | t- value | 1-sided NI p-value [b] | 1-sided superiority p-value | Estimate for difference and 2-sided 95% CI [c] |
|---|---|---|---|---|---|---|---|---|---|---|
| HDq12 (N=328) | 8.10 (0.61) | 8.77 (8.95) | 63.6 | 277 | 351.5 | HDq12-2q8 | 3.9881 | <0.0001 | 0.7447 | -0.57 (-2.26, 1.13) |
| HDq16 (N=163) | 7.23 (0.71) | 7.86 (8.38) | 61.4 | 149 | 315.0 | HDq16-2q8 | 2.7533 | 0.0031 | 0.9388 | -1.44 (-3.27, 0.39) |
| 2q8 (N=167) | 8.67 (0.73) | 9.21 (8.99) | 61.5 | 150 | | | | | | |

Abbreviations: 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; 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; DF=degrees of freedom; NI=non-inferiority; LS=least square; SE=standard error; SD=standard deviation

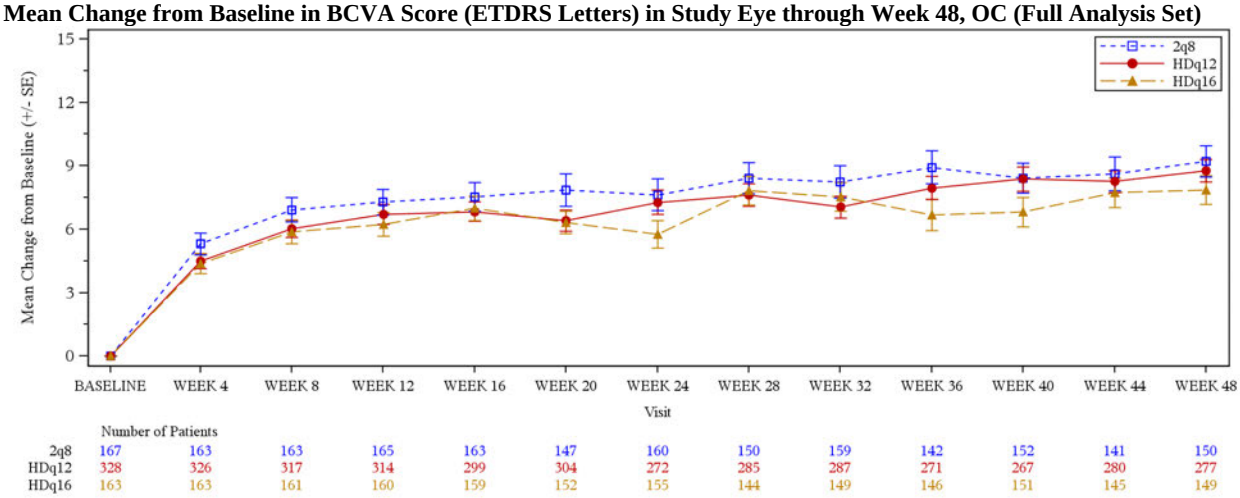
A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT (from reading center) [<400µm vs. ≥400µm], prior treatment for DME (per EDC; [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1).

[a] The contrast also included the interaction term for treatment x visit.

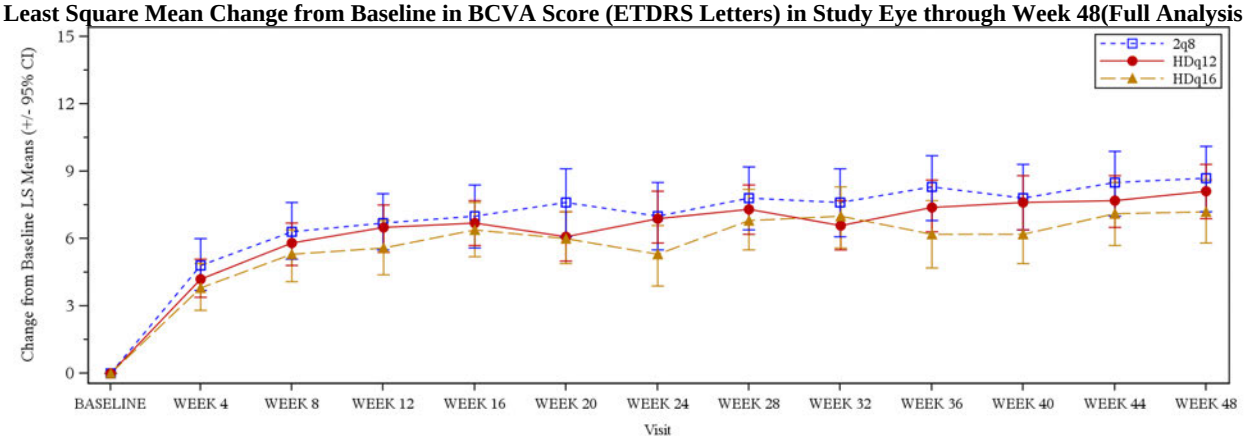
[b] p-value for the one-sided non-inferiority (NI) test at a margin of 4 letters.

[c] Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs. Source: PTT 14.2.1.1

**Mean Change from Baseline in BCVA Score (ETDRS Letters) in Study Eye through Week 48, OC (Full Analysis Set)**




**Least Square Mean Change from Baseline in BCVA Score (ETDRS Letters) in Study Eye through Week 48(Full Analysis Set)**




## Key Secondary Endpoint – Proportion of Participants with a ≥ 2-Step Improvement from Baseline in DRSS at Week 48 (LOCF) (Full Analysis Set)

| | Patients with a ≥ 2-step Improvement | Adjusted Difference (%) |
|---|---|---|
| **Treatment** | **From Baseline in DRSS, n (%)** | **2-sided (95% CI) [a]** |
| HDq12 (N=328) | 90/310 (29.0%) | 1.98 ( -6.61, 10.57) |
| HDq16 (N=163) | 30/153 (19.6%) | -7.52 ( -16.88, 1.84) |
| 2q8 (N=167) | 42/158 (26.6%) | |

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; 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.
Intercurrent events (ICE) were handled according to Table 1 of SAP (Appendix 16.1.9.1). LOCF= the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data. Patients were considered as non-responders if all post-baseline measurements were missing or non-gradable.
[a] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400 µm, ≥400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]). The non-inferiority margin was set at 15%. Missing or ungradable baseline was not included in the denominator. PTT 14.2.2.1

**Test Decisions and Statistical Conclusions for Global Analysis (Full Analysis Set)**

| Null hypothesis | p-value (one-sided) | Two-sided 95% CI | Test decision |
|---|---|---|---|
| Primary endpoint "Change from baseline in BCVA at Week 48" | | | |
| H10: non-inferiority of HDq12 vs. 2q8 in primary endpoint | $p < 0.0001$ | -2.26, 1.13 | Yes |
| H30: non-inferiority of HDq16 vs. 2q8 in primary endpoint | $p = 0.0031$ | -3.27, 0.39 | Yes |
| Key Secondary endpoint "Proportion of patients with a ≥2-step improvement in DRSS score" | | | |
| H50: non-inferiority of HDq12 vs. 2q8 in key secondary endpoint | NA | -6.61, 10.57 | Yes |
| H60: non-inferiority of HDq16 vs. 2q8 in key secondary endpoint | NA | -16.88, 1.84 | No, and hierarchical testing procedure stopped |
| Primary endpoint "Change from baseline in BCVA at Week 48" | | | |
| H70: superiority of HDq12 vs. 2q8 in primary endpoint | NA | | NA |
| H90: superiority of HDq16 vs. 2q8 in primary Endpoint | NA | | NA |

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; 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; CI=confidence interval; DRSS=Diabetic Retinopathy Severity Scale; NA= not applicable Source: PTT 14.2.1.1 and PTT 14.2.2.1

## 6.1. Statistical Review

**Extracted from the Statistical Review by Juan C. Vivar, Ph.D. and Solomon Chefo, Ph.D., Team Leader**

nAMD Indication

Although the total study duration is 96 weeks, efficacy and safety support in this BLA was based on the first 48 weeks of data. The main efficacy evaluation was based on BCVA assessed every 4 weeks through Week 96 as measured by the number of letters read at a starting distance of 4 meters (range: 0-100 letters). The primary efficacy endpoint was the change in BCVA from baseline at Week 48. The primary efficacy analysis was an evaluation of noninferiority of HDq12 or HDq16 to 2q8 in the primary efficacy endpoint on the full analysis set (FAS), including all randomized subjects who received at least one dose of study medication (see more details on the data handling approaches in Section **Error! Reference source not found.**). The noninferiority margin was set at -4.0 letters.

The treatment groups in PULSAR study were well balanced with respect to the demographic and baseline characteristics, in general. During the first 48 weeks of treatment, about 7% of subjects discontinued from the study and the discontinuation rates were comparable across the treatment groups.

In PULSAR study, both HDq12 and HDq16 treated subjects had a noninferior mean change in BCVA from baseline at Week 48 compared to 2q8 treated subjects. The adjusted mean change in BCVA from baseline at Week 48 was +6.1 letters in the HDq12 group, +5.9 letters in the HDq16 group, and +7.0 letters in the 2q8 group with treatment differences of -1.0 (95% CI: -2.9 to 0.9) for HDq12 vs. 2q8 and -1.1 (95% CI: -3.0 to 0.7) for HDq16 vs. 2q8. Although noninferiority in the primary endpoint was

established in the study, because of the frequent dosing, subjects that received aflibercept 2q8 displayed a numerical advantage in the BCVA gain from baseline through Week 48 compared to subjects that received the high dose of aflibercept.

**Adjusted Mean Change in BCVA from Baseline at Week 48 (FAS) (PULSAR)**

| Analysis Visit | | 2q8 (N = 336) | HDq12 (N = 335) | HDq16 (N = 338) |
|---|---|---|---|---|
| Baseline | Mean (SD) | 59.0 (14.01) | 59.8 (13.42) | 60.1 (12.40) |
| Week 48 | LS Mean (95% CI) | 7.0 (5.6, 8.5) | 6.1 (4.5, 7.6) | 5.9 (4.5, 7.3) |
| | Diff (95% CI) | --- | -1.0 (-2.9, 0.9) | -1.1 (-3.0, 0.7) |

Note: Adjusted mean changes in each treatment group and treatment differences (95% CI estimates) were based on MMRM method using FAS (See Section **Error! Reference source not found.** for details).

Sensitivity and supplementary analyses performed under different data handling strategies for missing data (including tipping point analysis) and intercurrent events were consistent with the primary efficacy results, leading to the same conclusion for a robust interpretation of the noninferiority findings.

Additionally, PULSAR study results for the proportion of subjects who had no retinal fluid at Week 16 established superiority of the pooled HD groups compared to 2q8 group. For example, at Week 16, 63% of subjects in the pooled HD groups had no retinal fluid compared to 52% of subjects in the 2q8 group with a treatment difference of 12% (95% CI: 5%, 18%). Although superiority was established at Week 16, the efficacy results were not consistent throughout the study. This was likely because treatment groups had variable dosing intervals after Week 16 and an increasing number of subjects in each treatment group exhibited fluid dryness in the immediate visit after injection was received. Thus, the clinical benefit of HD of aflibercept in retinal fluid dryness compared to 2q8 is questionable. The reviewer defers to the clinical review team for the clinical meaningfulness of this endpoint.

In summary, based on the collective efficacy evidence from the adequate and well controlled trial of PULSAR study, the reviewer concludes that the application for the nAMD indication provided substantial evidence for comparable efficacy benefit (BCVA gain) of aflibercept 8 mg administered every 12 weeks and every 16 weeks after three initial monthly doses compared to aflibercept 2 mg administered every 8 weeks after three initial monthly doses. However, the study did not establish consistent treatment benefit of the high doses of aflibercept in retinal fluid dryness compared to the active control.

DME/DR Indications

Although the total study duration is 96 weeks, efficacy and safety support in this BLA was based on the first 48 weeks of data. The main efficacy evaluation was based on BCVA assessed every 4 weeks through Week 96 as measured by the number of letters read at a starting distance of 4 meters (range: 0-100 letters) and based on diabetic retinopathy severity as measured by the diabetic retinopathy severity score (DRSS).

The primary efficacy endpoint was the change in BCVA from baseline at Week 48. The primary efficacy analysis was an evaluation of noninferiority of HDq12 or HDq16 to 2q8 in the primary

efficacy endpoint on the full analysis set (FAS), including all randomized subjects who received at least one dose of study medication (See more details in Section **Error! Reference source not found.**). The noninferiority margin was set at -4.0 letters.

The key secondary efficacy endpoint was the proportion of subjects with a ≥ 2-step improvement in DRSS at Week 48. This endpoint is intended to support the DR indication. The secondary efficacy analysis was an evaluation of noninferiority of each high dose group compared to the 2q8 group in the key secondary efficacy endpoint on the FAS. The noninferiority margin was set at -10%. Noninferiority in the key secondary endpoint was tested if noninferiority of both HDq12 and HDq16 to 2q8 in the primary endpoint was established.

The treatment groups in the PHOTON study were well balanced with respect to the demographic and baseline characteristics, in general (**Error! Reference source not found.**). During the first 48 weeks of treatment, about 7% of subjects discontinued from the study and discontinuation rates were comparable across the treatment groups (**Error! Reference source not found.**).

In PHOTON study, both HDq12 and HDq16 treated subjects had a noninferior mean change in BCVA from baseline at Week 48 compared to 2q8 treated subjects (**Error! Reference source not found.**). As shown, the adjusted mean change in BCVA from baseline at Week 48 was +8.1 letters in the HDq12 group, +7.2 letters in the HDq16 group, and +8.7 letters in the 2q8 group with treatment differences of -0.6 (95% CI: -2.3 to 1.1) for HDq12 vs. 2q8 and -1.4 (95% CI: -3.3 to 0.4) for HDq16 vs. 2q8. Although noninferiority in the primary endpoint was established in the study, because of the relatively frequent dosing, subjects that received aflibercept 2q8 displayed a numerical advantage in the BCVA gain from baseline through Week 48 compared to subjects that received either high dose of aflibercept (**Error! Reference source not found.**).

**Adjusted Mean Change in BCVA from Baseline at Week 48 (FAS) (PHOTON)**

| Analysis Visit | | 2q8 (N = 167) | HDq12 (N = 328) | HDq16 (N = 163) |
|---|---|---|---|---|
| Baseline | Mean (SD) | 61.5 (11.22) | 63.6 (10.10) | 61.4 (11.76) |
| Week 48 | LS Mean (95% CI) | 8.7 (7.2, 10.1) | 8.1 (6.9, 9.3) | 7.2 (5.8, 8.6) |
| | Diff (95% CI) | --- | -0.6 (-2.3, 1.1) | -1.4 (-3.3, 0.4) |

Note: Adjusted mean changes in each treatment group and treatment differences (95% CI estimates) were based on MMRM method using FAS (See Section **Error! Reference source not found.** for details).

Sensitivity and supplementary analyses performed under different data handling strategies for missing data and intercurrent events were consistent with the primary efficacy results, leading to the same conclusion for a robust interpretation of the noninferiority findings (**Error! Reference source not found.**).

Additionally, PHOTON study results for the key secondary endpoint of the proportion of subjects who achieved ≥ 2-step improvement in DRSS at Week 48 established noninferiority of HDq12 to 2q8 but not HDq16 to 2q8 using a noninferiority margin of -10% (**Error! Reference source not found.**). For example, at Week 48, 27%, 29%, and 20% of subjects in the 2q8, HDq12, and HDq16 treatment

groups, respectively, achieved ≥ 2-step improvement in DRSS from baseline to Week 48 with adjusted treatment differences of 2.0% (95% CI: -6.4%, 10.4%) for HDq12 versus 2q8 and -7.5% (95% CI: -16.8%, 1.8%) for HDq16 versus 2q8.

In summary, based on the collective efficacy evidence from the adequate and well controlled trial of PHOTON study, the reviewer concludes that the application for the DME indication provided substantial evidence for comparable efficacy benefit (in BCVA gain) of aflibercept 8 mg administered every 12 weeks and every 16 weeks after three initial monthly doses compared to aflibercept 2 mg administered every 8 weeks after five initial monthly doses.

For the DR indication, the application provided evidence for comparable efficacy benefit of aflibercept 8 mg administered every 12 weeks after three initial monthly doses compared to aflibercept 2 mg administered every 8 weeks after five initial doses. For this indication, the application did not provide evidence of comparable efficacy benefit of aflibercept 8 mg administered every 16 weeks after three initial doses compared to aflibercept 2 mg administered every 8 weeks after five initial doses.

# 7. Review of Safety

## 7.1. Deaths

**Candela**
There were no deaths during this study.

**Pulsar**

| Actual Treatment group | Subject identifier | Age/Sex/Race/ Study eye | Category/Location/Laterality | Study drug start date/Stop date | Date of death | AE (MedDRA preferred term) with fatal outcome | Start/Stop (relative to treatment) |
|---|---|---|---|---|---|---|---|
| 2q8 | (b) (4) | 96/F/W/L | Gastrointestinal/Abdominal Cavity/Other | (b) (6) | (b) (4) | Abdominal strangulated hernia | (b) (4) |
| 2q8 | | 83/M/A/L | Other/Lung/Right | | | Pneumonia aspiration | |
| 2q8 | | 83/M/W/L | Myocardial Infarction/Heart/Other | | | Cardiac arrest | |
| 2q8 | | 89/M/W/R | Symptomatic Skeletal Event/Skull/Other | | | Skull fracture | |
| 2q8 | | 69/M/W/L | Stroke/Cerebral Artery/Right | | | Cerebral infarction | |
| HDq12 | | 87/M/W/L | Immune-Related/Lung/Other | | | COVID-19 pneumonia | |
| HDq12 | | 81/F/W/R | Skeletal Related Event/Back/Left | | | Non-small cell lung cancer | |
| HDq12 | | 83/F/W/R | Tumor Lysis Syndrome/Liver Fissure/Other | | | Metastatic neoplasm | |
| HDq16 | | 91/F/W/R | Other/Unknown/Other | | | Death | |

AE Adverse event. MedDRA Medical Dictionary for Regulatory Activities. SOC System Organ Class. Race: A = Asian B = Black W = White AI = American Indian or Alaska Native NH = Native Hawaiian or Other Pacific Islander NR = Not Reported MUL=Multiple. Sex: F = female, M = male. Study eye: L = left, R = right; Relative to treatment start = date of death minus date of first study drug administration plus 1 day. Relative to treatment stop = date of death minus date of last study drug administration. 2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals. 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. MedDRA version 25.0. program location:/unblinded/bayer245919/stats/week48/primary/prog/listings/l_14_3_2_death.sas/15DEC2022/11:18

**Photon**

| Group | Patient ID | Age/Sex /Race | Date of First Treatment | Date of Last Treatment | Last Scheduled Visit | Last Scheduled Visit Date | Reason for Death/Date of Death |
|---|---|---|---|---|---|---|---|
| 2q8 | (b) (4) | 80/F/W | (b) (6) | (b) (4) | Week 16 | (b) (6) | Died of unspecified infection in Nursing Home (b) (4) |
| 2q8 | | 60/M/W | | | Week 32 | | Unknown/ (b) (4) |
| 2q8 | | 73/M/W | | | Week 36 | | Myocardial Infarction/ (b) (4) |
| 2q8 | | 60/M/W | | | Week 44 | | Cardiac Arrest/ (b) (4) |
| HDq12 | | 54/M/O | | | Week 36 | | Unknown/ (b) (4) |
| HDq12 | | 63/M/W | | | Week 12 | | Site was called on (b) (4) |
| HDq12 | | 70/M/W | | | Week 4 | | Cardiac Arrest due to Pneumoperitone UM suspected perforated duodenal ulcer/ (b) (4) |
| HDq12 | | 82/M/W | | | Week 4 | | Unknown/ (b) (4) |
| HDq12 | | 69/F/W | | | Week 4 | | Heart Attack (b) (4) |
| HDq12 | | 43/M/O | | | Week 32 | | Pneumonia (b) (4) |
| HDq12 | | 55/F/B | | | Week 16 | | Cardiac Arrest (b) (4) |
| HDq12 | | 82/F/W | | | Week 32 | | Unknown (b) (4) |
| HDq12 | | 70/F/B | | | Week 32 | | Ovarian Cancer (b) (4) |
| HDq16 | | 68/M/W | | | Week 40 | | Multiorgan Failure (b) (4) |
| HDq16 | | 65/M/W | | | Week 16 | | Unknown/ (b) (4) |
| HDq16 | | 51/M/W | | | Week 4 | | Chronic Respiratory Failure (b) (4) |

2q8: Aflib inistered every 8 weeks after 5 initial injections at 4-week intervals; 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. A=Asian, B=Black or African American, W=White, AI=American Indian or Alaska Native, NH=Native Hawaiian or other Pacific Islander, MU=Multiple; Date of first treatment=the date of the first study eye injection; Date of last treatment=the date of last administration of study medication (active [including rescue], sham, or fellow eye treatment)
/sasdata/Data/Production/BDM/VGFT/VGFT-HD-DME/VGFTe-DME-1934/Week48/Analysis_CSR/Programs/TFL/Generated/l_disc_16_2_1_2.sas (b) (6) 28OCT2022 10:39 SAS Linux 9.4)

## 7.2. Summary of Ocular Treatment-Emergent Adverse Events in the Study per

| **Adverse Reactions** | **PULSAR** | | | **PHOTON** | | |
|---|---|---|---|---|---|---|
| | **EYLEA HD q12** | **EYLEA HD q16** | **EYLEA 2q8** | **EYLEA HD q12** | **EYLEA HD q16** | **EYLEA 2q8** |
| | n=335 | n=338 | n=336 | n=328 | n=163 | n=167 |
| Cataract[a] | 4% | 4% | 4% | 3% | 6% | 3% |
| Conjunctival hemorrhage[a] | 3% | 2% | 1% | 4% | 4% | 4% |
| Intraocular pressure increased[a] | 4% | 4% | 2% | 3% | 1% | 4% |
| Ocular discomfort/eye pain/eye irritation[a] | 3% | 3% | 2% | 4% | 2% | 4% |
| Vision blurred[a] | 4% | 6% | 7% | 3% | 3% | 4% |
| Vitreous floaters[a] | 1% | 4% | 3% | 5% | 2% | 3% |
| Vitreous detachment[a] | 2% | 3% | 2% | 4% | 2% | 1% |
| Corneal epithelium defect[a] | 2% | 2% | 3% | 3% | 6% | 1% |
| Retinal hemorrhage | 3% | 3% | 4% | 0 | 4% | 1% |
| Intraocular inflammation[a] | 1% | 1% | 1% | 1% | 0 | 1% |

| | | | | | | |
|---|---|---|---|---|---|---|
| Retinal pigment epithelial tear/epitheliopathy[a] | 2% | 1% | 2% | <1% | 0 | 0 |
| Vitreous hemorrhage | <1% | 1% | 1% | 2% | 1% | 1% |
| Retinal Detachment[a] | 1% | <1% | 0 | <1% | 1% | 0 |
| Foreign body sensation in eyes[a] | 1% | 1% | 2% | <1% | 0 | 0 |
| Retinal pigment epithelial detachment[a] | 1% | 1% | 2% | 0 | 0 | 0 |

[a]Includes related terms

## 7.3. Immunogenicity

Immunogenicity was analyzed in the PULSAR and PHOTON studies using the Anti-drug antibody (ADA) analysis set and neutralizing anti-drug antibody (Nab) analysis set. The ADA analysis set included all participants who received study treatment and had at least 1 non-missing result in the ADA assay following the first study dose. The NAb analysis set included all participants who received any study treatment and were included in the ADA analysis set, tested negative at all ADA sampling times or tested positive at one or more post-dose ADA sampling times, and had at least one non-missing post-dose Nab result (either imputed or analysis result).

In the PULSAR study, the samples were taken at baseline and Week 48 visit. Treatment-emergent ADA responses were observed in 24 out of 793 participants at all dose levels. The incidence of treatment-emergent ADA in 2q8, HDq12, and HDq16 treatment groups during the 48-week period of treatment with intravitreally administrated aflibercept was 4/260 (1.5%), 11/269 (4.1%) and 9/264 (3.4%), respectively (Table 38 AMD). In each group the titers were low (<1000). None of the samples positive in the ADA assay demonstrated neutralizing activity. The safety profile of participants 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 participants with positive ADAs. Overall, no relevant impact of treatment-emergent ADAs on the safety profile could be observed (Module 5.3.5.1, PULSAR W48 CSR, Listings 16.2.7/3 and 16.2.8.1/5).

AMD: Number of participants with anti-drug antibodies to aflibercept at Week 48 (PULSAR, ADA analysis set)

| Category | 2q8 | HDq12 | HDq16 |
|---|---|---|---|
| | N=260 (100%) | N=269 (100%) | N=264 (100%) |
| ADA analysis set | 260 (100%) | 269 (100%) | 264 (100%) |
| Negative (a) | 249 (95.8%) | 250 (92.9%) | 250 (94.7%) |
| Pre-existing immunoreactivity (b) | 7 (2.7%) | 7 (2.6%) | 4 (1.5%) |
| Treatment-boosted (c) | 0 | 0 | 0 |
| Treatment-emergent positive (d) | 4 (1.5%) | 11 (4.1%) | 9 (3.4%) |
| Missing | 0 | 1 (0.4%) | 1 (0.4%) |
| Persistent | 0 | 0 | 0 |
| Indeterminate | 4 (1.5%) | 11 (4.1%) | 9 (3.4%) |
| Transient TE and TB Maximum Titer Category | 0 | 0 | 0 |
| Low (< 1000) | 4 | 11 | 9 |
| Moderate (1000-10000) | 0 | 0 | 0 |
| High (> 10000) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| NAb Analysis Set | 256 (98.5%) | 267 (99.3%) | 263 (99.6%) |
| NAb Negative | 256 (98.5%) | 267 (99.3%) | 263 (99.6%) |
| NAb Positive | 0 | 0 | 0 |

ADA = anti-drug antibody, Nab = neutralizing anti-drug antibody, TB = treatment-boosted, TE = treatment- emergent
See Definitions of terms for treatment arms description.

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 level
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.

Note: Percentages are based on ADA analysis set.
Source: Module 5.3.5.1, PULSAR W48 CSR, Tables 14.3.7/22, 14.3.7/23 and 14.3.7/24

In Photon, the incidence of treatment-emergent ADA in the 2q8, HDq12, and HDq16 treatment groups during the 48-week period of treatment with intravitreally administered aflibercept was 0/137 (0%), 3/263 (1.1%) and 2/141 (1.4%), respectively. No treatment-boosted (TB) 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 24 DME). The systemic safety profile of patients with treatment-emergent or pre-existing ADAs was reviewed for reactions potentially related to immunogenicity such as hypersensitivity, rash, pruritus, and urticaria. No such adverse events were reported in patients with positive ADAs. Overall, no relevant impact of treatment- emergent ADAs on the safety profile could be observed.

DME: Summary of ADA status, ADA category, maximum titer category, and NAb status by treatment group in participants with DME (PHOTON, ADA analysis set)

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

ADA = anti-drug antibody; n = Number of participants; NAb = neutralizing antibody; TE = Treatment-emergent; TB = Treatment-boosted; DME = Diabetic macular edema; Note: Percentages are based on ADA analysis set.
Source: Module 5.3.5.1, PHOTON W48 CSR, Appendix 16.1.14 CP Report, Table 10

## 8. Financial Disclosure

**Covered Clinical Study (Name and/or Number): Candela, Pulsar and Photon**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: >7500 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 55 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 50<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator in: 5<br>Sponsor of covered study: 0 | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☒ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☒ | No ☐ (Request explanation from Applicant) |

## 9. Systemic Blood Levels

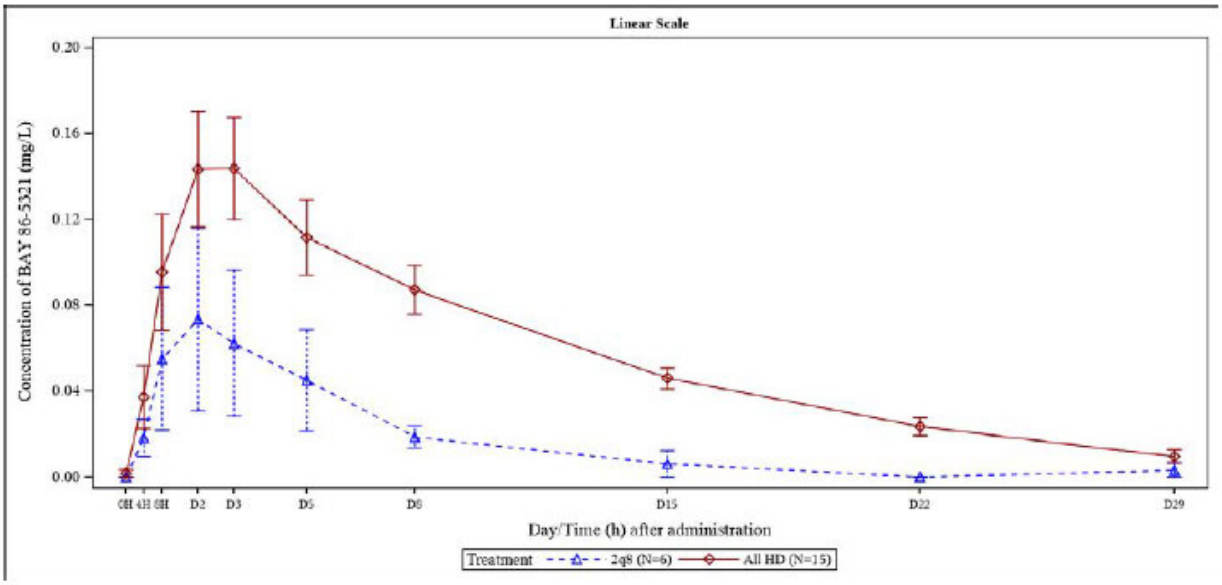
| | | | | Free aflibercept | | |
|---|---|---|---|---|---|---|
| **Treatment** | **Time** | **n total** | **n ≥ LLOQ** | **Geom. Mean ± SD** | **Arithm. Mean ± SD** | **Median** |
| 2q8 (N = 6) | Day 1, Pre-dose | 4 | 0 | N.C | 0.00 (0.00) | 0.00 |
| 2q8 (N = 6) | Day 1, 4 Hours Post-dose | 6 | 3 | N.C | 0.0182 (0.0210) | 0.0127 |
| 2q8 (N = 6) | Day 1, 8 Hours Post-dose | 5 | 4 | 0.03 (3.31) | 0.0549 (0.0742) | 0.0282 |
| 2q8 (N = 6) | Day 2 | 6 | 6 | 0.04 (2.68) | 0.0734 (0.105) | 0.0357 |
| 2q8 (N = 6) | Day 3 | 6 | 6 | 0.04 (2.49) | 0.0622 (0.0835) | 0.0320 |
| 2q8 (N = 6) | Day 5 | 6 | 5 | 0.03 (2.67) | 0.0451 (0.0580) | 0.0283 |
| 2q8 (N = 6) | Day 8 | 5 | 4 | 0.02 (1.66) | 0.0187 (0.0110) | 0.0212 |
| 2q8 (N = 6) | Day 15 | 5 | 1 | N.C | 0.00624 (0.0140) | 0.00 |
| 2q8 (N = 6) | Day 22 | 5 | 0 | N.C | 0.00 (0.00) | 0.00 |
| 2q8 (N = 6) | Day 29 | 5 | 1 | N.C | 0.00330 (0.00738) | 0.00 |
| HDq12 +HDq16 (n=13) | Day 1, Pre-dose | 12 | 0 | N.C | 0.00 (0.00) | 0.00 |
| HDq12 +HDq16 (n=13) | Day 1, 4 Hours Post dose | 13 | 6 | N.C | 0.0409 (0.0605) | 0.00 |
| HDq12 +HDq16 (n=13) | Day 1, 8 Hours Post dose | 12 | 9 | 0.05 (3.78) | 0.0973 (0.102) | 0.0672 |
| HDq12 +HDq16 (n=13) | Day 2 | 12 | 12 | 0.11 (2.21) | 0.146 (0.110) | 0.0903 |
| HDq12 +HDq16 (n=13) | Day 3 | 12 | 12 | 0.11 (2.06) | 0.137 (0.0947) | 0.112 |
| HDq12 +HDq16 (n=13) | Day 5 | 11 | 11 | 0.08 (1.86) | 0.0933 (0.0481) | 0.0854 |
| HDq12 +HDq16 (n=13) | Day 8 | 13 | 13 | 0.07 (1.75) | 0.0794 (0.0413) | 0.0682 |
| HDq12 +HDq16 (n=13) | Day 15 | 13 | 12 | 0.04 (1.76) | 0.0435 (0.0199) | 0.0385 |
| HDq12 +HDq16 (n=13) | Day 22 | 11 | 9 | 0.02 (1.76) | 0.0213 (0.0148) | 0.0232 |
| HDq12 +HDq16 (n=13) | Day 29 | 12 | 5 | N.C | 0.00766 (0.00958) | 0.00 |

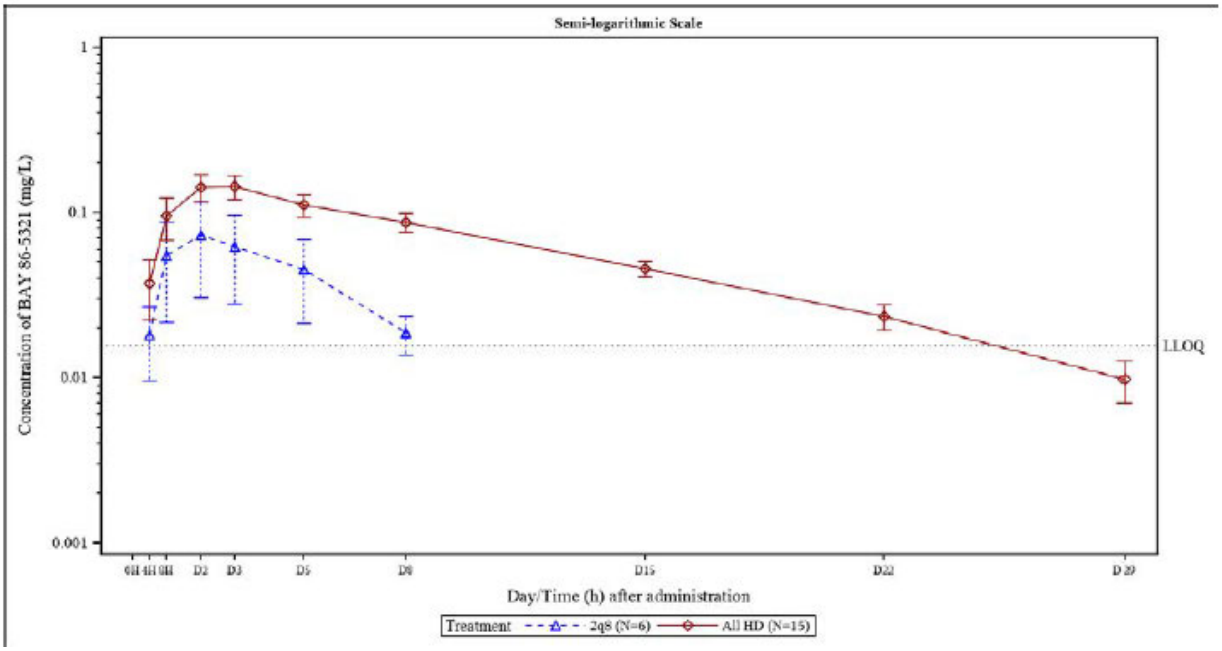
Arithm. = arithmetic, DPKS = dense pharmacokinetic analysis set, LLOQ = Lower level of quantification, geom. = geometric, N = Number of participants with unilateral treatment up to Week 48, n = Number of observations, nAMD = neovascular (wet) age- related macular degeneration, PK = pharmacokinetic, SD = 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. Minimum and Maximum have been rounded to 4 decimal places. See Definition of terms for treatment group description.
Source: Table 14.4/2.1 (post-hoc)

From the Clinical Pharmacology Review:
The clinical pharmacokinetics of HD aflibercept is summarized as below:

a. 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.
b. 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.
c. 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 Cmax and median Tmax 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.
d. 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.

e. Based on population PK covariates analysis, no dose adjustment is recommended by body weight, age, albumin, disease population, and race.
f. 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).
g. 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.



## 10. Advisory Committee Meeting

An Advisory Committee Meeting was not held to discuss this application. The application raised no new issues that were believed to benefit from an external discussion.

## 11. Labeling

The Physician's Package Insert that follows is based on a submission by Regeneron with modifications proposed by this reviewer and final revisions on June 23, 2023, by Regeneron as requested by the Agency. The Agency had no objection to the revised package insert.

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

## 12. Regulatory Action

Review of this application, as amended, has been completed. The Review Team has determined that we cannot approve this application in its present form. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product do not comply with the current good manufacturing practice regulations in parts 210 and 211. FDA conveyed deficiencies to the representative of the drug product manufacturing facility listed in this application following a pre-license inspection of the (b) (4) facility. Satisfactory resolution of the observations will be required before this BLA submission may be approved.

On (b) (4), the Agency received unsolicited information from (b) (4) For completeness, the OPQ assessment team performed an expedited review of this information and the team concluded (late (b) (4) that it does not impact their original recommendation.

The proposed proprietary name, Eylea HD was found conditionally acceptable during the current review cycle. The proposed proprietary name will need to be resubmitted when a response to the application deficiency is submitted.

A complete response action letter will be issued.

| | |
|---|---|
| William M. Boyd, MD | Deputy Division Director, Division of Ophthalmology. Dr. Boyd served as the Cross Discipline Team Leader for this application. |
| Wiley A. Chambers, MD | Division Director, Division of Ophthalmology |

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**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.**

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/s/

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WILEY A CHAMBERS
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WILLIAM M BOYD
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